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We love life, not because we are used to living but because we are used to loving.
~ Friedrich Nietzsche

With the onslaught of the COVID-19 pandemic as a silent but relentless adversary, our mantle, as frontliners, could not be tested more. Adapting to uncertainties on the ground and daily battles within ourselves of fulfilling our duty to defend our nation whilst being fully aware of the possible dangers that we and more importantly, our loved ones are exposed to.

However, for every worthy foe, an even greater champion is forged. A seasoned warrior called love strives at the battle front. Quietly manifesting through kind actions, faithful resilience and dedicated work towards the protection of lives, which we have the greatest love for.

Wordings by Dr Esther Tan Xi Xiang (NTFGH A&E)
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Editorial

World Kidney Day 2020: Advances in Preventive Nephrology

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Current international guidelines define chronic kidney disease (CKD) as decreased kidney function shown by glomerular filtration rate (GFR) of >60 mL/min per 1·73 m^2 and/or presence of markers of kidney damage for >3 months.[1] CKD patients are at risk of progression to end-stage kidney disease (ESKD), cardiovascular events and mortality.[2] Global CKD prevalence is high, ranging from 11–13%.[3] Globally, CKD-related death has increased by 28.8% from 2006 to 2016, resulting in 1.19 million deaths in 2016.[4]

In Singapore, the prevalence of CKD was reported to be 15.6% in 2007;[5] the prevalence of CKD in the diabetes population was even higher at 53%.[6] CKD prevalence is projected to increase to 24.3% by 2035 due to the rising incidence of diabetes mellitus, hypertension, higher detection rate and an ageing population.[7] CKD-related deaths in Singapore increased from 380 in 2016 to 638 in 2018, the 6th most common cause of death in Singapore.[8] The number of patients initiated on dialysis has increased from 901 (age-standardised rate [ASR] 190.4 per 1,000,000 population) in 2008 to 1300 (ASR 194.9 per 1,000,000 population) in 2017.[9] The most common causes of ESKD among incident dialysis patients in 2017 were diabetes mellitus (67.1%) and chronic glomerulonephritis (14.6%).[9]

CKD is a major public health problem in Singapore and it is timely that this year's theme for World Kidney Day focuses on the importance of preventive intervention to avert the onset and progression of kidney disease. Preventive interventions can occur at 3 levels: 1) primary prevention is introduced to prevent occurrence of CKD; 2) secondary prevention is introduced to reduce impact of CKD through earlier diagnosis and prompt treatment of early CKD; and 3) tertiary prevention is introduced to soften the impact of CKD by helping patients manage the complexity of CKD. This is the framework that the healthcare community in Singapore has adopted to combat the CKD epidemic.

Primary Prevention

Control of modifiable risk factors of CKD, especially diabetes mellitus and hypertension, remains the cornerstone in primary prevention of CKD. Diabetes mellitus is the most common cause of CKD in Singapore and the proportion of incident dialysis patients with diabetic kidney disease (DKD) has increased from 45.9% in 1999 to 67.1% in 2017.[9] In 2016, the Ministry of Health of Singapore announced that it had declared War on Diabetes since if nothing was done to prevent diabetes, the number of Singaporeans living with diabetes was projected to reach 1 million by 2050.[10] This initiative signified government leadership and support in preventing and managing diabetes in Singapore. The War on Diabetes was fought on several fronts in schools, supermarkets, food and beverage sector and local food industry to ensure the availability of healthier food choices to Singaporeans, as well as through large-scale programmes and collaborations with public agencies like Sport Singapore, People's Association and National Parks Board to increase accessibility of Singaporeans to physical activity. A national primary preventive programme against diabetes was a critical component in the primary prevention of CKD through the reduction of DKD incidence.

Strict control of glycaemia and blood pressure and the use use of renin-angiotensin system (RAS) blockade, sodium-glucose cotransporter 2 (SGLT-2) inhibitor and Dietary Approaches to Stop Hypertension diet have been shown to be beneficial in the primary prevention of CKD. The onset of persistent albuminuria (an early indication of CKD in at-risk populations) is commonly used as a primary outcome measure in CKD prevention studies. In a Cochrane review by Ruospo et al, strict glycaemic control (HbA1c <7%) was associated with a small clinical benefit in onset of albuminuria in diabetic patients, even though the long-term benefit of strict glycaemic control was uncertain.[11] In the population-based Atherosclerosis Risk in Communities

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Study, modest population-wide reductions in systolic blood pressure (SBP) were associated with fewer incident CKD events.[12] Both Bergamo Nephrologic Diabetes Complications Trial and Randomised Olmesartan and Diabetes Microalbuminuria Prevention Study found that the use of RAS blockade delayed onset of albuminuria in diabetic non-albuminuric patients.[13,14] In the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial, the use of SGLT-2 inhibitor was associated with lower rate of incident nephropathy.[15] A systemic review by Tahavi et al found that adherence to DASH diet was inversely associated with risk of CKD.[16]

Secondary Prevention

Patients are asymptomatic in the early stages of CKD. Hence, primary healthcare plays an essential role in secondary prevention of CKD by screening at-risk populations to diagnose early CKD. A systemic review by Komenda et al suggested that it was cost-effective to screen for CKD in patients with diabetes mellitus and hypertension.[17] Currently, primary healthcare doctors perform regular screening of renal panel and urine albumin to creatinine ratio in patients with hypertension and/or diabetes mellitus. In Singapore, a structured programme called Nephrology Evaluation, Management and Optimisation (NEMO) was launched by the National University Hospital and National Healthcare Group Polyclinics (NHGP) with support from the Ministry of Health to manage patients with DKD in NHGP. It commenced in April 2011 to evaluate patients with diabetes mellitus for DKD, optimise RAS blockade and DKD management and monitor its progression. In November 2013, NEMO reported an improvement or resolution of albuminuria in 40% of patients who completed the programme.[18]

In April 2017, the Holistic Approach in Lowering and Tracking CKD (HALT-CKD) programme was launched by the Ministry of Health. It was an expansion and extension of the NEMO programme and included all CKD patients in Singapore. It is an ongoing programme that aims to: 1) recruit and track all CKD stage 1–4 patients of any cause in every polyclinic; 2) slow down CKD progression with control of risk factors and RAS blockade in all CKD stages; and 3) encourage shared-care collaboration between primary healthcare and hospital renal physicians at CKD stage 3B–4. Accurate diagnosis and early initiation of treatment of underlying CKD cause, institution of RAS blockade, control of blood pressure and diabetes, avoidance of nephrotoxic agents, dietary (avoidance of high-protein diet >1.3 g/kg/day) and low salt intake (sodium <90 mmol or <2 g/day) and lifestyle modifications are some of the key aspects of slowing down CKD progression.[1] However, not all CKD patients are able to achieve these targets. For example, Teo et al reported that the mean protein intake of most CKD patients exceeded the recommended guidelines in a Singapore cohort.[19] Hence, one of the aims of HALT-CKD is to achieve and track the attainment of some of these measures in CKD patients in the polyclinics. Strong collaboration between primary healthcare physicians, hospital renal physicians and allied healthcare groups are needed to guide and educate CKD patients to achieve these aims.

After RAS blockade, the discovery of SGLT-2 inhibitor has shown great promise in slowing down CKD progression in recent trials. In the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation trial, SGLT-2 inhibitor demonstrated a lower risk of 30% of a composite endpoint (ESKD, doubling of serum creatinine level or death from renal or cardiovascular causes) in proteinuric diabetic patients who were already on RAS blockade at a median follow-up of 2.62 years.[20] Further studies are being conducted to examine SGLT-2 inhibitor effect on a wider range of GFR and non-diabetic CKD population.[21–3]

Treatment of the underlying cause of CKD is an important component in the secondary prevention of CKD, especially in patients with chronic glomerulonephritis. There has been much progress made in the management of chronic glomerulonephritis. The Kidney Disease: Improving Global Outcomes initiative organised a Controversies Conference on glomerular diseases in November 2017 with updates on the pathogenesis, workup and therapies for glomerulonephritis.[24,25] Such efforts will help to improve the outcomes of CKD patients with glomerulonephritis. More findings on potential biomarkers and therapies for the whole spectrum of glomerulonephritis are expected in the future.

Tertiary Prevention

Adverse clinical outcomes including ESKD, all-cause mortality and cardiovascular events are important considerations in management of CKD patients. Lower GFR and albuminuria are associated with worse cardiovascular outcomes, mortality and risk of ESKD.[26, 27] To lower the risk of adverse clinical outcomes, tertiary prevention of CKD involves continuation of CKD retardation measures and management of modifiable cardiovascular risk factors

and CKD complications. Accurate prediction of adverse clinical outcomes has gained much attention in recent years. With accurate prediction, more effort and focus can be given to the most susceptible CKD groups to improve their outcomes; timely education can also be provided to groups who have a high risk of progression to allow sufficient time to engage them on their long-term kidney care plans.

Tangri et al have proposed and validated a kidney failure risk equation (KFRE) model for progression of CKD to ESKD in a Canadian population and subsequently validated it in multinational cohorts.[28,29] Wang et al validated and recalibrated KFRE for improved performance in a Singapore cohort, although they did not have a validation dataset to confirm the improved performance of the recalibrated KFRE compared to the original KFRE model.[30] Grams et al proposed and validated a risk prediction model for the probability and timing of kidney failure that required kidney replacement therapy, non-fatal, non-fatal cardiovascular event and death from 29 cohorts in 30 countries.[31]

Blood pressure control and target in CKD population is widely discussed and investigated. For cardiovascular outcomes, the landmark Systolic Blood Pressure Intervention Trial (SPRINT) compared SBP <120 mmHg and <140 mmHg in a non-diabetic cohort, which included a CKD subgroup. The study demonstrated that patients with SBP <120 mmHg had better primary cardiovascular outcome (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.64–0.89) and all-cause death (HR 0.73, 95% CI 0.60–0.90).[32] It is to be noted that SPRINT measured SBP with automated devices (5-minute wait period and mean of 3 readings) and often in the absence of observers, which may result in readings that were lower than typical office blood pressure readings. This cardiovascular benefit for intensive blood pressure control is, however, less certain in diabetic and elderly CKD populations due to limitations in the design of study trials.[33,34] The effect of intensive blood pressure control in reducing ESKD risk is also less certain, but there is suggestion that intensive blood pressure control can protect CKD population against ESKD risk, especially in proteinuric CKD.[35]

Moving Forward

Research in CKD has advanced significantly in recent years. Apart from clinical parameters (GFR and proteinuria), more biomarkers that relate to the pathogenesis of CKD are needed to better predict CKD progression and develop targeted therapy. Worldwide, "omics" studies such as genomics, transcriptomics, metabolomics and proteomics are being conducted to better understand the disease biology and risk factors of CKD. In Singapore, the Diabetes Study in Nephropathy and other Microvascular Complications was launched in 2017 with the aim of improving the understanding of DKD and to reduce its prevalence by 30% over 5 years. It is the biggest local study to examine "omics" studies in DKD. Another area of interest is gut microbiome and gut-kidney axis and their association with CKD progression and cardiovascular risk. More results are expected in this area in the near future.

In the local renal and primary healthcare community, there is a move towards a collaborative population-based database to collect real-world data to improve the health and outcomes of CKD patients in Singapore. There is a role for more artificial intelligence-assisted prediction models with dynamic variables to more accurately predict the risk of non-CKD patients developing CKD in the future, and risks of CKD reaching ESKD, cardiovascular outcomes and mortality. Other areas of focus in research include CKD health service and qualitative research to investigate CKD work processes and CKD patients' perception to improve patient care, and value-based research to investigate the value of healthcare interventions from the perspectives of the patient, healthcare system and community.

With a deeper understanding of the causes and pathogenesis of CKD, there is a need to consider more public health measures to tackle some of the modifiable contributors to the disease burden of CKD which include diabetes, hypertension and obesity. War on Diabetes is a good start to create an impact on the changing landscape of CKD in Singapore, but more interventions can be considered. Mandatory reformulation of processed food to decrease their salt and sugar content, and salt and sugar taxes are some measures that can be considered. In a systemic review of dietary salt reduction policies by Hyseni et al, they found that population-wide policies such as mandatory reformulation generally achieved larger reductions in population-wide salt consumption than interventions that were directed at the individual.[36] Many countries had initiated sugar tax for sugar-sweetened beverages and this was associated with a mean decline in beverage purchases and dietary intake of 10.0%.[37] We can consider a comprehensive multi-pronged intervention that involves mandatory reformulation and sugar and salt tax, in addition to the current education media campaign and food labelling. The financial gain from sugar and salt

taxes can be awarded to industry players who comply with mandatory reformulation, provide infrastructure and subsidies to industry players who provide healthy food (such as high efficiency urban vegetable farms) or exercise (such as gyms) and the general public who comply with the healthy lifestyle campaign. With the high penetration rate of smartphone use in the local population, compliance to healthy lifestyle by the general public can be tracked and duly rewarded.

These are exciting times in the management of CKD with new discoveries of its pathogenesis, diagnostics and therapies. Strong and sustained collaborative efforts by all stakeholders are critical to maintain the initiatives designed to improve the health and outcomes of CKD population in Singapore. Recent national primary preventive programmes like War on Diabetes will also likely have a major impact on the changing landscape of CKD in Singapore. However, it will take decades before we know whether any of these advances prove meaningful. As Johann Wolfgang von Goethe once said, "What is not started today is never finished tomorrow". On this World Kidney Day 2020, we can make an impact on CKD by acting together as a nation.

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3: 1–150.
2. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 164:659–63.
3. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease–a systematic review and meta-mnalysis. PLoS One 2016;11:e0158765
4. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1151–210.
5. Sabanayagam C, Lim SC, Wong TY, Lee J, Shankar A, Tai ES. Ethnic disparities in prevalence and impact of risk factors of chronic kidney disease. Nephrology Dialysis Transplantation 2010;25:2564–70.
6. Low SK, Sum CF, Yeoh LY, Tavintharan S, Ng XW, Lee SB et al. Prevalence of chronic kidney disease in adults with type 2 diabetes mellitus. Ann Acad Med Singapore 2015;44:164–71.
7. Wong LY, Liew AST, Weng WT, Lim CK, Vathsala A, Toh MPHS. Projecting the burden of chronic kidney disease in a developed country and its implications on public health. Int J Nephrol 2018;2018:5196285.
8. Ministry of Health, Singapore. Principal causes of death 2016–2018. Available at: https://www.moh.gov.sg/resources-statistics/singapore-health-facts/principal-causes-of-death. Accessed on 24 February 2020.
9. National Registry of Diseases Office, Singapore. Singapore Renal Registry Annual Report 2017. Available at: https://www.nrdo.gov.sg/publications/kidney-failure. Accessed on 24 February 2020.
10. Ministry of Health, Singapore. War on Diabetes Summary Report 2016–2019. Available at: https://www-moh-gov-sg-admin.cwp.sg/docs/librariesprovider5/war-on-diabetes/wod_public_report.pdf. Accessed on 24 February 2020.
11. Ruospo M, Saglimbene VM, Palmer SC, De Cosmo S, Pacilli A, Lamacchia O, et al. Glucose targets for preventing diabetic kidney disease and its progression. Cochrane Database Syst Rev 2017;6:CD010137.
12. Hardy ST, Zeng D, Kshirsagar AV, Viera AJ, Avery CL, Heiss G. Primary prevention of chronic kidney disease through population-based strategies for blood pressure control: the ARIC study. J Clin Hypertens 2018;20:1018–26.
13. Ruggenenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, et al. Preventing microalbuminuria in type 2 diabetes. N Engl J Med 2004; 351:1941–51.
14. Haller H, Ito S, Izzo Jr JL, Januszewicz A, Katayama S, Menne J, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 2011;364:907–17.
15. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–34.
16. Taghavi M, Sadeghi A, Maleki V, Nasiri M, Khodadost M, Pirouzi A, et al. Adherence to the dietary approaches to stop hypertension-style diet is inversely associated with chronic kidney disease: a systematic review and meta-analysis of prospective cohort studies. Nutr Res 2019;72:46–56.
17. Komenda P, Ferguson TW, Macdonald K, Rigatto C, Koolage C, Sood MM, et al. Cost-effectiveness of primary pcreening for CKD: a systematic review. Am J Kidney Dis 2014;63:789–97.
18. National Healthcare Group Polyclinics, Singapore. NEMO slows kidney function decline in diabetic patients. Transform Care 2013, Issue 3. Available at: https://www.nhgp.com.sg/uploadedFiles/NewsLetter/2010/Transform%20Care%20Issue%203.pdf. Accessed on 24 February 2020.
19. Teo BW, Toh QC, Xu H, Yang AY, Lin T, Li J, et al. Dietary protein intake in a multi-ethnic Asian population of healthy participants and chronic kidney disease patients. Ann Acad Med Singapore 2015;44:145–9.
20. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019 Med 2019;380:2295–306.
21. Neuen BL, Jardine MJ, Perkovic V. Sodium-glucose cotransporter 2 inhibition: which patient with chronic kidney disease should be treated in the future? Nephrol Dial Transplant 2020;35:i48–55.
22. Heerspink H, Stefansson BV, Chertow GM, Correa-Rotter R, Greene T, Hou FF, et al. Rationale and protocol of the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial. Nephrol Dial Transplant 2020;35:274–82.
23. Herrington WG, Preiss D, Haynes R, von Eynatten M, Staplin N, Hauske SJ, et al. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. Clin Kidney J 2018;11:749–61.
24. Floege J, Barbour SJ, Cattran DC, Hogan JJ, Nachman PH, Tang S, et al. Management and treatment of glomerular diseases (part 1): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2019;95:268–80.
25. Rovin BH, Caster DJ, Cattran DC, Gibson KL, Hogan JJ, Moeller MJ, et al. Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2019;95:281–95.
26. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration

rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010;375:2073–81.

27. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int 2011;80:93–104.
28. Tangri N, Stevens LA, Griffith J, Tighiouart H, Djurdjev O, Naimark D, et al. A predictive model for progression of chronic kidney disease to kidney failure. JAMA 2011;305:1553–9.
29. Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. JAMA 2016 2016;315:164–74.
30. Wang Y, Nguyen FNHL, Allen JC, Lew JQL, Tan NC, Jafar TH. Validation of the kidney failure risk equation for end-stage kidney disease in Southeast Asia. BMC Nephrol 2019;20:451.
31. Grams ME, Sang Y, Ballew SH, Carrero JJ, Djurdjev O, Heerspink H, et al. Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. Kidney Int 2018;93;1442–51.
32. Wright Jr JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco, MV, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–16.
33. Garrison SR, Kolber MR, Korownyk CS, McCracken RK, Heran BS, Allan GM. Blood pressure targets for hypertension in older adults. Cochrane Database Syst Wright Jr JT, Rev 2017;8:CD011575.
34. Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–85.
35. Lv J, Ehteshami P, Sarnak MJ, Tighiouart H, Jun M, Ninomiya T, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ 2013;185:949–57.
36. Hyseni L, Elliot-Green A, Lloyd-Williams F, Kypridemos C, O' Flaherty M, McGill R, et al. Systematic review of dietary salt reduction policies: evidence for an effectiveness hierarchy? PLoS One 2017;12:e0177535.
37. Teng AM, Jones AC, Mizdrak A, Signal L, Genç M, Wilson N. Impact of sugar-sweetened beverage taxes on purchases and dietary intake: systematic review and meta-analysis. Obes Rev 2019;20:1187–204.

Original Article

Laparoscopic Tubal Re-anastomosis or In Vitro Fertilisation in Previously Ligated Patients: A Comparison of Fertility Outcomes and Survey of Patient Attitudes

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Abstract

Introduction: We aim to compare live birth rates, cost analysis and a survey of patient attitudes between laparosopic tubal re-anastomosis and IVF. Materials and Methods: *Retrospective study*: A retrospective study was done in a single reproductive medicine and IVF unit in Singapore, from January 2011 to December 2016. Previously ligated patients underwent either laparoscopic tubal re-anastomosis or IVF. The primary outcome was first live birth after treatment. Interval to first pregnancy, miscarriage and ectopic pregnancies were also reported. *Survey*: Patients attending the subfertility clinic completed a questionnaire on IVF and tubal re-anastomosis, on preferred choice of treatment, before and after reading an information sheet. Results: *Retrospective study:* 12 patients underwent tubal re-anastomosis while 31 patients underwent IVF treatment. Pregnancy (75.0% vs 35.5%) and live birth (58.3% vs 25.8%) were significantly higher in the tubal surgery group (P<0.05%) after transferring all available embryos in one stimulated IVF cycle. Cost per live birth was lower in the tubal surgery group (SGD27,109 vs SGD52,438). *Survey:* One hundred patients participated in the survey. A majority of patients preferred tubal surgery to IVF (68.2% vs 31.8%) before given information on the procedures, but indicated a preference for IVF (54.6%) to surgery (45.4%) after receiving information on the procedures. Conclusion: For women less than 40 years of age, desiring fertility after tubal ligation, laparoscopic tubal re-anastomosis offers better live birth rates and cost-effectiveness. Patients in Singapore are equivocal as to their preference after education regarding the choices. Thus laparoscopic tubal re-anastomosis remains a viable alternative to IVF treatment.

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Key words: Artificial reproductive technology, Laparoscopic tubal reversal, Previous tubal ligation

Introduction

Tubal ligation remains a common method of contraception, despite the availability of multiple other reversible methods.[1] A sizeable proportion (up to 30%) of women who undergo sterilisation seek fertility after the procedure, for reasons such as a new marriage, regret, or loss of a child.[2,3] For these women, the options are either tubal reversal surgery or IVF.

Conventionally, microsurgical tubal reversal was performed via a laparotomy. However, in the past few decades, surgeons have increasingly used laparoscopy to perform this procedure, with equivalent outcomes.[4] With the relative ease of access to In Vitro Fertilisation (IVF) technologies and the high technical skills required for tubal re-anastomosis, there has been an increase in the use of (IVF) techniques and a consequent decline in surgical tubal reversal. However, a recent ASRM committee opinion paper posited that surgical tubal re-anastomosis is a feasible alternative to IVF for previously ligated patients.[5] With the advancement in IVF techniques and success rates, the role of tubal reversal in the management of this group of women needs to be re-evaluated.

We have previously published on the outcome of tubal reversal surgery, and showed similar fertility outcomes in women undergoing laparotomy and laparoscopic tubal

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reversal surgery (Tan and Loh).[6] Here we aim to compare the outcomes between laparoscopic tubal anastomosis and IVF in women with previous tubal ligation in a single Reproductive Medicine and IVF unit. In addition, we wanted to gain a better understanding of the attitudes and perceptions of patients with regards to the 2 treatment options.

Materials and Methods

Retrospective Study

We conducted a retrospective review of all cases with previous tubal ligation, who underwent subsequent fertility treatment from January 2011 to December 2016, in a single Reproductive Medicine and IVF unit in Singapore.

All couples underwent standard fertility assessment, namely history, pelvic examination, semen analysis, ultrasound scans of the pelvis and determination of ovarian reserve. A non-directive counseling of the option of laparoscopic tubal reversal or IVF were offered when there are no contraindications to either treatment modalities.

The primary outcome measure is the time to first live birth after tubal reversal surgery, or the transfer of all available embryos generated through 1 stimulated cycle of IVF accordingly. Patients are censored after a live-birth, with further frozen embryo transfers and pregnancies after the first live birth excluded. Ectopic pregnancies, miscarriages, duration of surgery and hospitalisation were also reported. A cost-benefit analysis was performed. Exclusion criteria were: other sub-fertility factors such that natural fertility was unlikely (fibroids distorting endometrium, endometriosis, severe adenomyosis, oligo- or asthenozoospermia, female partner aged 40 years and above) patients with unilateral anastomosis, and anti-mullerian hormone levels (AMH) <1. All laparoscopies were performed by the same surgeon. IVF patients were under the management of a team of doctors, and were followed up until transfer of all embryos (up to 10 months) and first resulting live birth, up to 24 months. Tubal reversal patients were followed up for 24 months post-surgery. Institutional IRB approval was granted for this study.

IVF Protocol

All patients on the IVF arm underwent controlled ovarian stimulation (COS) on day 2 of their menses, after an ultrasound scan to exclude the presence of a dominant follicle (>9mm diameter). This was achieved using recombinant FSH and/or human menopausal gonadotrophin at doses of 150 to 450 units, for 8 to 14 days. Gonadotrophin-releasing hormone (GnRH) antagonist was started after 5 days of COS. When two or more leading follicles have reached 17mm in diameter, Ovidrel 250mc was used to trigger final follicular maturation, with oocyte retrieval performed 34 to 36 hours later. Embryos generated were transferred in the fresh cycle if there were no contraindications, with supernumerary embryos transferred in subsequent frozen cycles. Up to 2 cleavage stage embryos or blastocysts were transferred, at the attending physician's discretion, with luteal phase support achieved with vaginal progesterone for 4 weeks post embryo transfer (Crinone 8% gel twice daily). A Clinical Pregnancy was registered where a intrauterine gestation sac with a fetal pole was seen at 4 weeks post ET. Live birth data was gathered from the ART registry at the hospital.

Surgical Technique

The surgery was carried out via 4-port laparoscopy in a typical configuration: 5mm ports at umbilicus bilateral iliac fossa, and suprapubic area. Both fallopian tubes were surveyed and the point of ligation, be it through the Pomeroy method or application of Filshie clips, was excised. Instillation of a vasoconstrictor (Pitressin diluted in normal saline) was performed through a 26G spinal needle into the meso-salpinx around the ligated region. This served to hydro-dissect the peritoneal layers from the muscular layer of the fallopian tubes, and maintained a blood-free operating field. A uterine manipulator was then inserted to allow for hydrotubation. The scarred segment of the tubes were first identified and resected until healthy ends of the tube could be identified, with good patency as evidenced by the free flow of methylene blue dye from the proximal resection point upon hydrotubation. For the distal tubal segment, the lumen was identified, cannulated proximally and injected with methylene blue with a hollow probe, to ensure free flow of dye through the fimbrial end. The mesosalpinx was approximated with 3O polyglactin suture if the tubal segments were too far apart to aid in the anastomosis. A single-layer, two-stitch technique was utilised for re-anastomosis with 6-0 PDS sutures placed at the 12 and 6 o'clock positions of the tube. The suture was passed through the muscularis and mucosa in a single plane. Successful re-anastomosis is evidenced by free flow of methylene blue through the fimbrial end at hydrotubation. Leakage of dye through the anastomotic site is commonly seen and does not indicate failed re-anastomosis, as long as dye flows through the fimbrial end.

Statistical Analysis

Statistical analysis between groups was performed using chi-squared tests and Fisher's exact test for non-parametric parameters. A value of $P < 0.05$ is considered statistically significant.

Survey

A survey of patient preferences between the 2 treatment methods was conducted. Patients attending the sub-fertility clinic in the same tertiary institution in Singapore, were approached for participation. Survey forms were given out in the waiting area and collected before the patient left the clinic. A total of 100 patients were surveyed. The questionnaire can be divided into 3 main components: demographics, information on both IVF and laparoscopic tubal re-anastomosis (including treatment overview, success rates, costs and complications), and the choice of treatment before and after reading the information.

Results

Retrospective Study

There were 31 patients in the IVF group and 12 patients in the tubal reversal surgery group. The baseline characteristics of the 2 groups were largely similar (Table 1). Transfer of all fresh and frozen embryos derived from one IVF stimulation cycle was completed within 4.5 months (range 3.0–10.0 months).

Table 1. Comparison of baseline characteristics between IVF and tubal reversal (patient age <40 years old)

	IVF (n = 31), mean (SD)	Tubal Reversal (n = 12), mean (SD)	P Value
Age	35 (4)	34 (4)	0.546
BMI	23.0 (4.8)	23.4 (3.2)	0.790
Parity	2.8 (1.1)	2.6 (0.8)	0.468
AMH	4.2 (3.2)	5.7 (1.4)	0.148

AMH: Anti-mullerian hormone level; BMI: Body Mass Index; IVF: In vitro fertilisation; SD: Standard deviation

Table 2 shows the outcome for all patients. The pregnancy rate (PR) was higher in the tubal-reversal group, up to 1 year after surgery, than the IVF group, 75% (9/12) vs 35.5% (11/31) (P = 0.039). The live birth rate (LB) was also higher after tubal-reversal surgery compared with the IVF group 58.3% (7/12) vs 25.8% (8/31) (P = 0.045). The miscarriage rates were similar, with 1 ectopic pregnancy in the surgery group (11.1%) and none in the IVF group. In the IVF group, there was a single case of twins (9.1%) and 2 cases of clinically important ovarian hyperstimulation syndrome (OHSS) (6.5%); neither of these events occurred in the tubal-reversal group. The mean number of embryos transferred was 1.9 and 1.3 for cleavage stage and blastocyst stage respectively (Table 3).

In the surgical arm, 9 patients were ligated by Filshie clips (75.0%), 2 patients by the Pomeroy method (16.7%), and one by Falope Rings (8.3%). All the patients who underwent tubal reversal surgery were discharged the next day, except for one patient who was discharged on the same day. The mean (standard deviation [SD]) duration of surgery was 156 (SD 20) minutes. The mean (SD) interval from surgery to conception was 3.9 (SD 4.8) months (Fig. 1).

Cost Analysis

The estimated costs of IVF in our centre are as f ollows: fresh cycle SGD12,500, frozen embryo transfer SGD4000. A total of 31 fresh and 8 thaw cycles were performed, with 8 live births resulting in the IVF

Table 2. Comparison of outcome measures between IVF and tubal reversal (patient age <40 years old)

	IVF (n = 31)	Tubal reversal (n = 12)	P value
Pregnancy rate	35.5% (11/31)	75.0% (9/12)	0.039
Miscarriage rate	27.3% (3/11)	11.1% (1/9)	1.0
Ectopic rate	0% (0/11)	11.1% (1/9)	0.279
Live birth rate	25.8% (8/31)	58.3% (7/12)	0.045
Multiple rate	9.1% (1/11)	0% (0/11)	1.0
OHSS rate	6.5% (2/31)	0% (0/12)	

IVF: In vitro fertilisation; OHSS: Ovarian hyperstimulation syndrome

Table 3. Number of embryos transferred (mean)

	Mean number of embryos transferred
Cleavage stage	1.9
Blastocyst	1.3

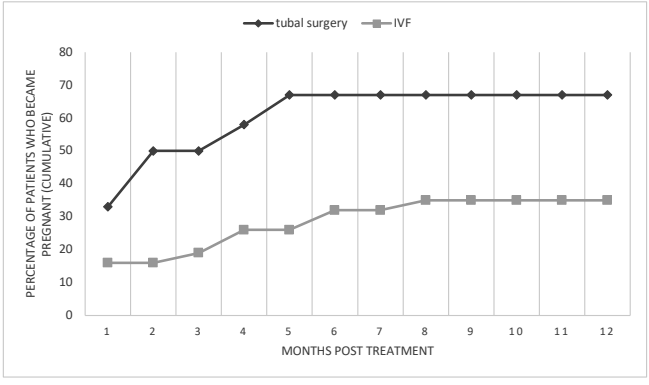

Figure 1. Interval to pregnancy post-treatment (months)

group. The average bill for a tubal reversal procedure with one day hospitalisation is SGD15,132. As ectopic pregnancy is the main complication of this surgery, the cost of treatment (SGD8180) is included in this analysis. 12 patients underwent tubal reversal and one patient underwent treatment for ectopic pregnancy, with a resultant 7 live births. This puts the cost of a live birth at SGD52,438 for the IVF group, which is approximately double that of the surgery group (SGD27,109). We have omitted to include the additional costs of OHSS treatment for 2 patients, complications for multiple pregnancies, loss of days from work, as these complications can be largely mitigated with the use of agonist triggering and freeze-all strategies in high risk patients, and the transfer of single blastocysts. These findings are in agreement with many other studies, which show that tubal surgery is more cost-effective in patients below 37 to 40 years of age.[6,7,8]

Survey

A total of 100 patients participated in the survey. 12 forms were incompletely filled and excluded from analysis. The mean age of the patients was 35.1 (SD 3.6) years. More than half (64.8%) of the patients were nulliparous, 28.4% had one child, and 6.8% had 2 or more children. Majority of the respondents (77%) attended university and stayed in government housing (71%) (Table 4).

Table 4. Baseline characteristics of survey participants

Age	Number of participants (n=88)	Chose IVF **BEFORE** reading information (n=28)	Chose surgery **BEFORE** reading information (n=60)
• <35	38 (43%)	18 (47%)	20 (53%)
• 35 and above	50 (57%)	10 (20%)	40 (80%)
Parity			
• 0	55 (62%)	21 (38%)	33 (62%)
• 1 and above	33 (38%)	7 (21%)	27 (79%)
Housing			
• Public housing	62 (71%)	22 (35%)	40 (65%)
• Private property	26 (29%)	6 (23%)	20 (77%)
Education level			
• Did not attend university	20 (23%)	8 (40%)	14 (60%)
• Degree or higher	68 (77%)	20 (29%)	46 (71%)

Before reading the information sheet, 28 (31.8%) patients preferred IVF and 60 (68.2%) preferred surgery (Table 5). After having read the information, more patients indicated a preference for IVF (54.6%) to surgery (45.4%). We found that younger patients under 35 years of age are just as likely to choose surgery as IVF, while older women had a preference for tubal surgery, particularly after information was given. Parity, housing type and educational level had less of an impact on patient choice. There was no significant difference in baseline characteristics between participants who chose the same option and those who chose a different treatment option after reading the information.

Table 5. Treatment choices before and after reading information

	n (%)
Treatment choice **BEFORE** reading information	
• IVF	28 (31.8%)
• Tubal surgery	60 (68.2%)
Treatment choice **AFTER** reading information	
• IVF	48 (54.6%)
• Tubal surgery	40 (45.4%)

Conclusion

In this paper, we sought to determine the relevance of tubal reversal surgery a decade after our initial publication[6]. This is of rising importance as more women seek fertility treatment post-sterilisation. The changing dynamics of the financing model for IVF treatment in Singapore, and the rising incidence of re-marriages (22.7% of all marriages in 2017) also contribute to this trend. We found that the cumulative pregnancy rates were largely similar at 75% by 18 months (58% live births), compared with 68% by 48 months in the previous cohort where both open and laparoscopic approaches were utilised. These datasets compare favourably to other published data (pooled PR 65%).[9]

Our results show that both pregnancy and live birth rates in the surgery group were roughly double that of the IVF group after the completion of one stimulated IVF cycle. Since there was no significant difference in the mean age between the 2 groups, the miscarriage rates were similar as expected. The main complication of tubal reversal is ectopic pregnancy (1 case in the surgery group vs none in the IVF group). The risk of ectopic pregnancies after surgical reversal has been shown to be raised by up to 3-fold (pooled data 5.6%).[6,9,10,11] In our study, the ectopic occurred in a patient at very

high risk because of narrowed tubal lumen as seen at surgery. However, this is offset by the risk of multiple pregnancies and OHSS in the IVF group. Another advantage of surgery over IVF is that patients can try to conceive in every cycle without further treatment, with the possibility of more than one pregnancy being achieved. In fact, 2 of the patients in the surgery group went on to have more than one child.

This is a good prognosis cohort with proven fertility, with tubal ligation as their only infertility diagnosis. The pregnancy (35.5%) and live birth (25.8%) rates in the IVF group are largely similar to the 27% LBR according to the HFEA database for patients of the same age group, encompassing all diagnoses.[12]

Prognostic Factors for Tubal Reversal

A number of prognostic factors have been studied, including method of sterilisation, BMI, interval between sterilisation to reversal and age.[13–19] Only age has been consistently found to affect success rates. Women 40 years and older should undergo proper counselling so that they can have realistic expectations of their fertility, whichever method they choose.

Although no difference has been found in reversal success among the different sterilisation methods, the numbers studied are small. It is intuitive that techniques like the Filshie clip, which destroy the smallest portion of the tube, will be more amenable to reversal. It is possible that with the more destructive surgical approaches, there is not enough healthy tube left to reconstruct, and surgery may not be attempted at all.

Benefits of Laparoscopic Surgery

Laparoscopic tubal reversal surgery is a technically challenging operation, requiring advanced endoscopic training and experience.[14] However, it confers clear benefits over laparotomy, in terms of faster patient recovery and shortened hospitalisation stay of 1 day (in our series) versus 3 to 6 days where laparotomy had been employed.[4,6] Laparoscopic tubal reversal was also initially thought to have inferior pregnancy rates compared to laparotomy.[20,21] This has been refuted in numerous studies.[4,6,9,21] Another commonly cited advantage of laparotomy over laparoscopy is shorter operating times.[4,6,22] In our study, the mean operating time is 156 minutes. Compared to time taken for laparotomy (range 128–160 minutes),[4,6] the difference is not large. There is a well-documented learning curve for this surgery, of approximately 10–15 cases, whereby the operating time is shortened considerably.[4,6,21,23] In a previous study consisting of 9 cases, the mean operating time was 195 minutes; this has shortened to an average of 156 minutes in the our 12 cases.

Surgical complications have been shown to be rare. There were no instances of complications in our study. In a large cohort of 202 laparoscopic tubal reversal patients, there was only one report of venous thrombosis in the lower leg, reported as likely secondary to patient positioning.[14] Another unintended outcome is conversion to laparotomy, which has been quoted at 5.3% in another study.[14] There were no cases of laparotomy conversion in our study.

In the hands of an experienced surgeon, laparoscopic tubal reversal is a safe operation, with acceptable operating times, good success rates and rapid patient recovery times.

Interval to Live Birth

This is a vital consideration for patients pursuing fertility, as oocyte number and quality decrease with advancing maternal age. A couple who fails to get pregnant after tubal re-anastomosis can be offered IVF; the question is how soon after surgery do we start to consider IVF. A large cohort study has found cumulative live birth rates of 21% by 1 year, 40% by 2 years and 50% by 5 years after tubal re-anastomosis.[24] Similarly, our study found an average interval of 3.9 months (range 1–18 months) from surgery to pregnancy, with a cumulative live birth rate of 58.3% by 18 months. Thus, a couple can reasonably try naturally for pregnancy for 12–18 months, before moving on to IVF if unsuccessful.

Due to the much longer follow up period (80 months) in the surgery group compared to the IVF group (19 months), there is a question of bias in favour of the surgery group. In our study, this is less of a concern, as almost all the patients in the surgery group conceived within 6 months.

Survey

This survey is done on a population of sub-fertile patients. It would have been more relevant to survey patients who have been ligated and now seek fertility treatment, but will take a long time to accrue a number of such patients.

This survey highlights the initial reluctance of patients to undergo IVF. This may be due to the general public's poor understanding or misconceptions about IVF. They may feel that IVF is an unnatural process, excessively costly or raises the rates of congenital defects. Surgery on the other hand, restores normal anatomy and function, and may be more acceptable to the patients. However, after reading the information, a large proportion of patients eventually choose IVF, showing that attitudes and perceptions

can be changed when non-directive information has been given.

In our survey, patients who chooses surgery initially tend to be older than 35 years of age, have at least one child, and live in private housing. Multiparous women are likely to be more confident of their own natural fertility, and thus will lean towards surgery. Being older, they may be more wary of new technology. Conversely, respondents younger than 35 are more likely to choose IVF initially. They may be more willing to try new methods and embrace new technology.

The results of this and other studies clearly show that tubal reversal is significantly more successful than IVF in patients aged <40 years. This is stated in the information given to patients. In spite of the lower success rates, a large proportion of patients still choose to undergo IVF after reading the information provided. This illustrates the importance of patient autonomy and counselling to enable them to make well-informed choices. Success rate may be the most foremost consideration for the clinician, but it may not be the most important for the patient.

Limitations

The retrospective nature and small sample sizes limit the generalisation of this study. However, our results are largely in keeping with other published reports of cost-effectiveness of tubal reversal over IVF in young patients, and the success rates of laparoscopic tubal reversal.

Conclusion

For a woman below 40 years old, desiring fertility after tubal ligation and with no other sub-fertility factors, laparoscopic tubal reversal may offer better pregnancy and live birth rates, and may be more cost-effective compared to IVF. Patients in Singapore have a preference for tubal reversal particularly if they are older and have received non-directive counselling of both approaches.

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REFERENCES

1. Zurawin RK, Ayensu-Coker L. Innovations in contraception: a review. Clinical obstetrics and gynecology 2007;50:425–49.
2. Schmidt JE, Hillis SD, Marchbanks PA, Jeng G, Peterson HB. Requesting information about and obtaining reversal after tubal sterilization: findings from the U.S. Collaborative Review of Sterilisation. Fertil Steril 2000;74: 892–8.
3. Curtis KM, Mohllajee AP, Peterson HB. Regret following female sterilization at a young age: a systematic review. Contraception 2006 Feb;73(2):205–10.
4. Cha SH, Lee MH, Kim JH, Lee CN, Yoon TK, Cha KY. Fertility outcome after tubal anastomosis by laparoscopy and laparotomy. J Am Assoc Gyn Laparosc 2001;8:348–52.
5. The Practice Committee of the American Society for Reproductive Medicine. Role of tubal surgery in the era of assisted reproductive technology: a committee opinion. Fertil Steril 2015 Jun;103(6):e37–43.
6. Tan HH, Loh SF. Microsurgical reversal of sterilisation—is this still clinically relevant today? Ann Acad Med Singapore 2010;39:22–26.
7. Messinger L, Alford C, Csokmay J, Henne M, Mumford S, Segars JH, Armstrong AY. Cost and efficacy comparison of in vitro fertilization and tubal anastomosis. Fertil Steril 2015;104(1):32–8.e4.
8. Boeckxstaens A, Devroey P, Collins J, Tournaye H. Getting pregnant after tubal sterilisation: surgical reversal or IVF? Hum Reprod 2007;22:2660–2664.
9. Van Seeters JAH, Chua SJ, Mol BWJ, Koks CAM. Tubal anastomosis after previous sterilisation: a systematic review. Hum Reprod Update 2017;23:358–370
10. Bissonnette F, Lapensee L, Bouzayen R. Outpatient laparoscopic tubal anastomosis and subsequent fertility. Fertil Steril 1999;72:549–52.
11. Dubuisson JB, Chapron CL, Nos C, Morice P, Aubriot FX, Garnier P. Sterilisation reversal: fertility results. Hum Reprod 1995;10:1145–51.
12. Fertility treatment 2014–2016 — Trends and figures. Human Fertilisation and Embryology Authority. March 2018
13. Kim SH, Shin CJ, Kim JG, Moon SY, Lee JY, Chang YS. Microsurgical reversal of tubal sterilisation: a report on 1,118 cases. Fertil Steril 1997;68:865–870.
14. Yoon TK, Sung HR, Kang HG, Cha SH, Lee CN, Cha KY. Laparoscopic tubal anastomosis:fertility outcome in 202 cases. Fertil Steril 1999;72:1121–1126.
15. Hanafi MM. Factors affecting the pregnancy rate after microsurgical reversal of tuballigation. Fertil Steril 2003;80:434–440.
16. Gordts S, Campo R, Puttemans P, Gordts S. Clinical factors determining pregnancy outcome after microsurgical tubal reanastomosis. Fertil Steril 2009;92:1198–1202.
17. Schepens JJ, Mol BW, Wiegerinck MA, Houterman S, Koks CA. Pregnancy outcomes and prognostic factors from tubal sterilisation reversal by sutureless laparoscopical re-anastomosis: a retrospective cohort study. Hum Reprod 2011;26:354–359.
18. Berger GS, Thorp JMJr, Weaver MA. Effectiveness of bilateral tubotubal anastomosis in a large outpatient population. Hum Reprod 2016;31:1120–1125.
19. Reich H, McGlynn F, Parente C, Sekel L, Levie M. Laparoscopic tubal anastomosis. J Am Assoc Gynecol Laparosc 1993;1:16 –9.
20. Katz E, Donesky BW. Laparoscopic tubal anastomosis. A pilot study. J Reprod Med 1994;39:497– 8.
21. Koh CH, Janik GM. Laparoscopic microsurgical tubal anastomosis: results of 40 consecutive cases. In: Program and abstracts of the 52nd Annual Meeting of the American Society for Reproductive Medicine. Boston, MA. November 2, 1996.
22. Hawkins J, Dube D, Kaplow M, Tulandi T. Cost analysis of tubal anastomosis by laparoscopy and by laparotomy. J Am Assoc Gynecol Laparosc 2002;9:120–124.
23. Malacova E, Kemp-Casey A, Bremner A, Hart R, Stewart LM, Preen DB. Live delivery outcome after tubal sterilisation reversal: a population-based study. Fertil Steril 2015;104:921–926

Original Article

Recovery in Psychosis: Perspectives of Clients with First Episode Psychosis

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Abstract

Introduction: Recovery from psychosis relates to connectedness, hope for the future, identity, meaning in life and empowerment. The process of recovery is often described as gradual and non-linear, with many stages and turning points, and without a definitive end point. This qualitative study aims to understand what recovery means to clients, to better understand their unique recovery process and what helps in recovery among clients with lived experience of first episode psychosis (FEP) in a developed Asian setting. Materials and Methods: The study design and interview guide development included inputs from persons with psychosis, following which 7 focus group discussions were conducted with 40 FEP clients of a tertiary care psychiatric institute. Results: Thematic qualitative analysis identified three themes: 1) meaning of recovery (where participants expressed their views on what recovery meant to them); 2) recovery as a journey (due to the constant ups and downs in the long process of recovery, it was often articulated as a "journey"); and 3) facilitators of recovery (related to resources, practices and experiences that supported their recovery). Conclusion: The emergent themes provide an understanding of the meaning of recovery to persons with FEP, their experiences as they proceed with their recovery journey and factors they found helpful. The importance of acceptance of the condition and the personal role the individual plays in his or her own recovery was evident in the narratives of the participants. The study suggests a need to incorporate recovery-relevant approaches right from the first episode of psychosis.

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Key words: Meaning of recovery, Qualitative, Thematic analysis

Introduction

The treatment of serious mental illnesses such as schizophrenia and related psychoses has dramatically shifted in the last century. In the early 1900s, asylums were the standard form of care for patients with serious mental illnesses.[1] It was the advent of the first psychotropic drugs such as chlorpromazine in the 1950s that precipitated "deinstitutionalisation" or the shift from large central psychiatric state hospitals to community-based care.[2] In the last few decades, there has been increasing support to re-examine our existing model of recovery from mental illnesses from the traditional clinical model of recovery to one that complements it with a more holistic, service user-centred and recovery-oriented approach.[3–5] The consequent reform to the delivery of mental health care has already emerged in Australia and the United Kingdom.[6]

The traditional clinical definition of recovery from schizophrenia has primarily been focused on symptom remission.[7] This definition of recovery is predicated on: 1) lessening the severity of psychopathological symptoms,

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2) improvements in psychosocial functioning; and 3) a minimum duration of meeting criteria 1) and 2).[8] This can be labelled as an outcome-based definition of recovery. Service users, however, have often defined recovery as one that goes beyond an outcome-based definition. In a systematic review by Leamy et al,[9] the themes of connectedness, hope and optimism for the future, identity, meaning in life and empowerment were found to be associated with personal recovery. This definition of recovery, which can be called the process-based definition of recovery, is well described by Anthony[10] as "a deeply personal, unique process of changing one's attitudes, values, feelings, goals, skills, and/or roles. It is a way of living a satisfying, hopeful, and contributing life even with limitations caused by the illness. Recovery involves the development of new meaning and purpose in one's life as one grows beyond the catastrophic effects of mental illness". There are important clinical implications if service users do not hold onto the same model of recovery as health systems in terms of treatment services to be delivered to service users and their quality of life and user satisfaction.

Service users have defined recovery as recovery from an illness recovery perspective (reduction, elimination or control over their psychotic symptoms), but also from a psychological and personal recovery perspective (understanding the illness, accepting the illness as part of the self and regaining a sense of "self" that existed before illness onset) and social and functional recovery perspective (having a positive social identity through meaningful relationships and also finding meaningful employment).[11] Recovery has been often described as a gradual and non-linear process with many stages and turning points[12] without a definitive end point.[13] Recovery from psychosis has also been described as an ongoing process of dealing with the illness on a day-to-day basis and overcoming challenges as they come without any enduring state of recovery.[14] An investigation of the factors that might contribute to or facilitate recovery from a service user's perspective provides valuable information to policymakers who are attempting to improve service user's satisfaction and quality of life. A study by Law et al[15] found that service users had cited social support, knowledge of their illness and self-care and availability of mental healthcare resources as important factors that helped them in their recovery.

Most studies that investigated the concept of recovery from the perspective of service users were in Western populations. There is a lack of studies on Asian populations. In one of the few studies conducted in Asia (to the best of our knowledge) by Lam et al[16] in Hong Kong, participants' concept of recovery extended from regaining previous functions (both cognitive and social) to gaining a stronger sense of control over their lives. In Singapore, previous research found that positive re-appraisal, better social support, shorter duration of hospitalisation and higher education are associated with better quality of life and, possibly, recovery in patients with schizophrenia.[17] There is, however, a need for further research in Asian populations with multiethnic groups to investigate whether the findings from Western populations can be replicated in Asia. This, again, will have important implications in the delivery of treatment suited to the idiosyncratic needs of the population.

This study aimed to understand what recovery means to clients with lived experience of psychoses by using a qualitative approach in a tertiary psychiatric hospital in Singapore. Additionally, clients' perspectives on the process of recovery from psychosis were sought, along with what specifically persons with psychoses found helpful in their recovery.

Materials and Methods

Ethics

Ethical approval for the study was obtained from the Domain Specific Review Board of the National Healthcare Group of Singapore. Written informed consent was obtained from all participants and from a parent, legally accepted representative or next-of-kin for participants who were aged <21 years old (the age of majority in Singapore).

Study Population and Setting

The inclusion criteria for the study participants were clients from outpatient clinics run by the Early Psychosis Intervention Programme (EPIP) in the Institute of Mental Health, Singapore.[18] EPIP clients are provided phase-specific multidisciplinary care that includes appropriate psychopharmacological management, psychotherapy, occupational therapy and group interventions as necessitated. Additionally, every client is assigned a case manager who, via a strengths-based approach, provides supportive counselling, psychoeducation and bridges the various services and maintains contact with them to ensure appropriate care through different phases of their illnesses.[18]

The study participants were EPIP clients aged between 18–40 years old who were able to speak and understand English and were deemed clinically stable by their treating team (doctor or case manager) to participate in focus group discussions (FGDs). Potential participants were referred to members of the research team by the treating team. Members of the research team (who were not directly

responsible for providing care for the potential participant) then approached them to participate in FGDs.

A total of 40 participants took part in 7 FGDs that were conducted from May 2017 to January 2018. Each FGD comprised 5–6 participants and lasted between 60–90 minutes. All participants were reimbursed with SGD60 each for their time and travel.

Data Collection

A FGD guide was developed alongside service users with a history of psychosis (Fig. 1). A member of the study team, who was also a service user with psychosis, sought inputs from 2 peers while determining the content and language of the FGD guide. All FGDs were conducted in a community centre outside the hospital by 2 team members, a facilitator and a note-taker, who had experience in qualitative research. Participants who agreed to take part in the study were informed of their rights and responsibilities as a study participant and their consent was obtained for the start of FGDs. The facilitators (MS, JAV, YYL and LC) were researchers who were not involved in the direct care of the participants for the FGDs that they individually facilitated. After discussions among the authors, an interview guide was developed and used to facilitate the FGDs to ensure consistency across different discussions. The FGDs encompassed a set of probes directed to elicit responses from participants on what recovery from psychosis meant to them, how they (would) describe their recovery, what they found helpful in their recovery and how other influences might have impacted both their recovery and their views on recovery.

There seems to be no general rule on the optimum number of focus groups to have in order to generate the maximum number of themes from the FGDs. Guest et al[19] found that 90% of all the themes in their study were discoverable within 3–6 focus groups. However, the generalisability of their findings might still be dependent on factors such as the homogeneity of the sample. In our study, there was relative uniformity, with all the sample experiencing psychosis for <3 years, and with some differences in socioeconomic and educational backgrounds. Study team members met after every FGD to discuss and review data that was generated in an iterative process. After 7 FGDs, it was decided that no new themes were emerging, and that data saturation had been reached. As such, no further FGDs were conducted. All FGDs were audio-recorded and transcribed verbatim. The transcripts were cross-checked with the facilitator for consistency. Participant confidentiality was maintained by excluding all possible identifying information such as names from the transcripts.

Data Analysis

A qualitative thematic analysis methodology was used to elicit meaning from the data collected and to establish themes.[20] Using an inductive approach, content of the interviews was coded to allow themes of importance to emerge from the data. The researchers first familiarised themselves with the transcripts by reading through them several times to obtain a broader perspective of what the participants were saying in the FGDs. Subsequently, a code book was developed for data analysis based on the narratives of the transcripts.[21] A team member with experience of psychosis was involved in the development of the code book and interim coding process and reviews. Coding of all transcripts was performed by 2 researchers (JV and LC) after establishing good inter-rater reliability (0.77 kappa coefficient). Themes were subsequently derived based on the codes from the transcripts. The coding and thematising of data were conducted using NVivo software version 11.

Results

Background of Participants

Participants were aged 18–39 years old with a mean age of 27 years. There were more participants who were women (67.5%), of Chinese ethnicity (65%), never married (95%) and with a polytechnic or other diploma (30%). The sociodemographics of the participants are shown in Tables 1 and 2. All participants were clients of EPIP.

Focus group discussion guide

- What does recovering from a mental condition mean to you?
- When someone says they have recovered from a mental condition, what does it mean to you?
- When does one consider himself/herself in recovery?
- What is your personal goal in terms of recovery?
- When you were first diagnosed with a problem, what were your thoughts/feelings about recovery? Did they change over time? Can you describe your experiences?
- What do you feel/ think about recovery now?
- How can one reach recovery from a mental condition?
- What, according to you, does your recovery mean to your family members/relatives?
- What, according to you, does your recovery mean to the doctors and others treating you?

Fig. 1. Focus group discussion guide.

Most of them self-reported having schizophrenia or other psychoses with a wide variation in their duration of illness which ranged from 5 months to 6 years; 25 (62.5%) of the 40 participants were first diagnosed within <2 years before the FGDs.

Key Themes

From the content of the FGDs, 3 main themes related to recovery from psychosis emerged: 1) meaning of recovery (where participants expressed their views on what recovery meant to them); 2) recovery as a journey (due to the constant ups and downs in the long process of recovery, it was often articulated as a "journey") and 3) facilitators of recovery (related to resources, practices and experiences participants attributed as being helpful in their recovery). Although there were interrelations and overlaps between themes—which were deliberated upon by the study team—these were eventually deemed to signify different contexts, specifically meaning, process and influences, respectively, and hence retained as separate themes. However, to put the findings in perspective and understand these relations, a broad concept map was developed from the content (Fig. 2).

Table 1. Sociodemographics of Study Participants

Variable	N	%
Median age in years (range)	27 (18–39)	
Gender		
Men	13	32.5
Women	27	67.5
Ethnicity		
Chinese	26	65.0
Malay	4	10.0
Indian	9	22.5
Others	1	2.5
Marital status		
Never married	38	95.0
Married	2	5.0
Education		
GCE "O"/"N" level/completed secondary education	4	10.0
Vocational institute/NITEC certificate	9	22.5
Polytechnic/other diploma	12	30.0
GCE "A" level/completed pre-university or junior college	6	15.0
University degree	8	20.0
Postgraduate degree (e.g., Masters/PhD)	1	2.5

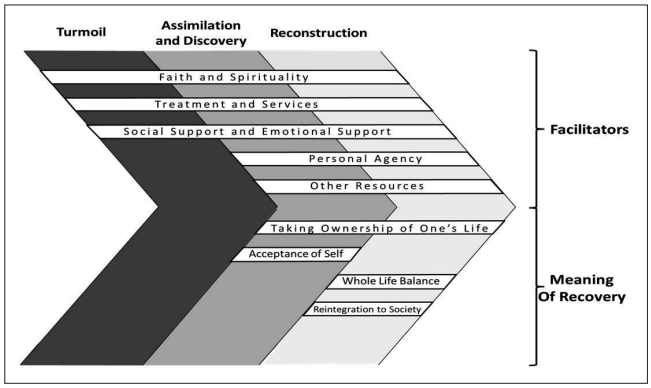

Figure 2: Concept map of recovery-related themes

One: Meaning of Recovery

Four secondary themes on the definition of recovery came up during the FGDs. These were acceptance of self, taking ownership of one's life, whole-life balance and reintegration into society.

Acceptance of Self

Acceptance came up as a strong theme in FGDs. To the participants, "recovery means also accepting who we are". Being able to move forward despite their illness was crucial to them. With this acceptance, they are able to start over in life again and "to try again and again". This involved a change in the outlook on their lives. It may be accepting that they may have to change their initial goals. It also meant that they were able to pursue their interests and hobbies. All in all, it was about being able to accept themselves and "turn to more positives in life" to make the best of the situation that was thrown their way.

From FGD 1: "I think recovery means you find peace in yourself and then you start believing in yourself to get things back in track."

Taking Ownership of One's Life

Having control and independence were expressed as key elements in our participants' recoveries. They voiced the importance of being "back on [their] own feet" and being able to "handle things himself or herself". The locus of control ranged from not being reliant on external factors to being able to handle challenges at the workplace, and to manage everyday activities such as commuting and going to the movies. A participant noted that "many people live on and live good meaningful lives, even with

Table 2. Background of Participants

Identification Number	Age (Years)	Gender	Ethnicity	Diagnosis*
1	20	Woman	Chinese	Psychosis
2	27	Woman	Chinese	Psychosis
3	24	Woman	Chinese	Bipolar disorder
4	25	Man	Chinese	Schizophrenia
5	25	Woman	Malay	Brief psychotic disorder
6	36	Woman	Chinese	Schizophrenia
7	39	Woman	Chinese	Schizophrenia and anxiety disorder
8	21	Man	Chinese	Schizophrenia
9	20	Woman	Others	Schizophrenia and obsessive compulsive disorder
10	22	Man	Indian	Schizophreniform disorder
11	31	Man	Chinese	Depression with psychotic features
12	21	Woman	Chinese	Schizophrenia and obsessive compulsive disorder
13	25	Woman	Chinese	Bipolar disorder with psychosis
14	27	Man	Malay	Bipolar disorder
15	32	Woman	Chinese	Psychosis
16	29	Woman	Indian	Schizophrenia
17	33	Woman	Chinese	Undisclosed
18	21	Woman	Chinese	Schizophrenia
19	21	Woman	Chinese	Psychosis
20	36	Woman	Indian	Bipolar disorder with psychosis
21	24	Woman	Chinese	Bipolar disorder
22	27	Man	Chinese	Undisclosed
23	25	Man	Chinese	Schizophrenia
24	29	Woman	Chinese	Schizoaffective disorder
25	27	Man	Malay	Brief psychosis with affective symptoms
26	35	Woman	Indian	Psychosis
27	18	Man	Chinese	Undisclosed
28	20	Woman	Indian	Attenuated psychotic disorder
29	24	Man	Chinese	Undisclosed
30	26	Woman	Chinese	Depression
31	26	Man	Chinese	Schizophrenia
32	28	Woman	Malay	Schizoaffective disorder
33	24	Man	Malay	Schizophreniform disorder
34	34	Woman	Chinese	Psychosis
35	39	Woman	Malay	Schizophrenia
36	24	Woman	Chinese	Mild delusional disorder
37	23	Woman	Other	Psychosis with anxiety depression
38	25	Woman	Chinese	Bipolar disorder
39	23	Man	Malay	Psychosis
40	37	Woman	Chinese	Bipolar disorder

*Self-reported by participants

symptoms". To them, it was about having the freedom to make decisions that were not based on their fears and disabilities, but to pursue their hopes and dreams.

From FGD 7: "[Recovery] starts when a person starts taking ownership of their health … I would define a person [who] will start having recovery when they begin to take charge of their own life, their own health, taking deliberate steps towards moving towards recovery, and not depending just on people around them."

Whole-Life Balance

Most participants also highlighted the importance of symptom remission and regaining function as a definition of recovery. They cited the ability to function in regular daily life as recovery. Focusing on whole-life balance, participants mentioned simple things such as eating normally, socialising normally and managing emotional well-being as part of symptom remission. Besides symptom remission, being able to "control mood and temper" also came up as an important aspect of recovery.

From FGD 6: "A recovered person should be physically well, mentally stable, emotionally stable."

Reintegration into Society

For most participants, recovery was about reintegrating back into the society in their age-appropriate roles (school, family or work). For instance, a participant shared that she fell ill halfway through her internship. Now that she's back in school, "completing [her] internship is very important". Going back to their previous roles at home, in school or at work was crucial to their recovery. Some of the participants also perceived being able to reduce and eventually stop their medication as relevant to their reintegration.

From FGD 2: "To me [recovery] will look like they have stopped medication and they resume to their previous roles in society like they have gone back to work, gone back to school, whatever they have been doing previously."

Two: Recovery as a Journey

Recovery was perceived to be a "journey" by a number of participants who felt there was no specific end goal or a fixed final destination for them. Each journey was believed to be a very personal experience with a unique trajectory for each individual. A few participants mentioned that it was a journey they took more than once.

As narrated by 1 participant from FGD 4: "So after my second recovery, I realised that recovery is not final and that like what you said about the journey, to extend the metaphor, like the paths are very meandering, sometimes there are many fault paths and sometimes we even meet cliffs and all that. So there's a lot of internal and external so-called traps and obstacles to your own recovery, and sometimes you just have to find another way around it. There is no one fixed-route."

Three distinct phases in their recovery journey were described by participants during FGDs. First, the phase of "turmoil" which the participants went through when they had their first episode of psychosis and recovery seemed a very distant destination. Second, the phase of "assimilation and discovery" which started as participants described coming to terms with their condition, slowly accepting it, understanding it and started working on it. Third, the phase of "reconstruction" when participants began building and utilising their personal, social and external resources towards their recovery.

Turmoil

Participants shared experiences of the time when they had their first episode of psychosis. A number of them shared being "hit out of the blue" with minimal prior signs and insight into the condition. They described being very scared, confused, in chaos and denial and feeling hopeless about the possibility of recovery at this stage. Expressions of anxiety, disbelief, anger, guilt and withdrawal were common across the participants and FGDs. Many found themselves in conflict with themselves, their families and at times with the treating clinical teams.

From FGD 1: "When I first heard voices and all that, I felt very fearful. I felt like somehow or rather it's as bad as though the world is going to end. That kind of fear I felt. Very fearful, even to my case manager or my own mom. I was very afraid of like what's going to happen."

From FGD 4, "When you are first hospitalised and you are so isolated in your own ward or you don't even know what the heck is happening to you, it's very hard to even conceive for recovery or to conceive that you are … you are just totally in denial, or like it's just very hard press … everything is like a confused jumble around you, so you just cannot conceive anything more than whatever is in front of you, whatever you are facing right now."

Some of them expressed having very low self-esteem during this period and feeling desperate to get better soon and recover as fast as they could without specifically knowing what this entailed.

From FGD 4: "We think no hope. No hope, really no hope. How can we recover, we are so desperate to get well, but it's very difficult to get well."

However, a small number of participants also described being relieved when they knew exactly what was happening to them and felt that was a turning point in their journey even while they were still quite unwell.

From FGD 5: "I think I was aware for a while that there's something going on. At first I thought it was like a stress disorder or something. For the longest time I thought I was depressed. So I saw a counsellor for that. A lot of the symptoms you realise that it's similar, you know? Low energy, lack of happiness, distrustful. It really didn't occur to me that it could be something psychiatric in nature. So when this thing came, like he said I was quite relieved. Cos only through diagnosis can we treat it."

Assimilation and Discovery

This phase in the journey was described by participants as the time when they started accepting their condition. Many of them mentioned that since their first experience with psychosis, they had accepted that they were a different person "than their past self", the change in their circumstances as they now "had this illness" and that the illness was a part of them.

From FGD 1: "It's like a journey because we are no longer the same people as how we are used to be. So it's about adapting to changes. And trying to like adjust our needs more."

From FGD 6: "It's more about coming to terms with the experience itself and I think taking ownership over the experience. I think for me I would have actually recovery … the term recovery if let's say I would say 'yeah it happened to me but I'm fine with it.' You know, this is part of who I am and I am also able to then move past it."

With this acceptance came the need to develop insight into their diagnosis. Many read about mental disorders and available treatments on their own, discussed with peers and clinicians, or attended talks and/or therapy to find out more about what to expect and how to deal with such situations.

From FGD 1: "It's also being aware of like your diagnosis, like what is the illness, what does it actually mean. So I tried to like find out more about like this illness and see how it relates to me."

This period was also perceived as period of "discovery" and "self-reflection" where participants started discovering more about their illness, themselves, their "limits" and what triggers maladaptive behaviours in them and about life in general.

From FGD 1: "It's about being authentic. Because I think that when you are being true to yourself, you are able to see where are your limits and from there you can know what are the more proper treatments for you."

From FGD 3: "I started to have, for some people it may seem delusional, but for me there are some things that I discovered or been through things like that like, to me recovery was that being able to make sense of everything that was what I thought of recovery" and "I just feel like going through this whole experience has made me discover the much more human side, aspect of life la. That's what I feel la, life is fragile, it's very delicate. That's what I discovered."

Reconstruction

As the participants transitioned from acceptance of their illness and discovering themselves, they described their onward "bumpy" journey towards rebuilding their lives. A "loop" of dealing with ups and downs was expressed. This included their experiences of slowly going back to the society they belonged to and re-forming their identity and place. Participants mentioned that dealing appropriately with day-to-day issues they face such as personal challenges, stigma and medication side effects formed a considerable part of their recovery journey.

From FGD 1: "I slowly found the motivation to slowly go back to society."

From FGD 6: "Family, friends, sometimes your employers also, your colleagues. They tell you to get off medication, to them it's an expectation of recovery but it's not realistic. And it affects you because it affects your sense of self and what you are able to do."

From FGD 3: "I gained like 13 kg ever since I was being placed on (name of medication). Yeah, so now I'm trying to lose all the weight I gained. And then it also caused me to have insomnia and no appetite."

Reconstructing their life included a number of players and factors, and the different roles and contribution each had in the participants' journey. These included taking medications, seeking advice and support from professionals and drawing strength from close relationships.

From FGD 3:"Take your medication, that would be number one. Make sure you have a very supportive circle of people that are around you so that you'll be able to recover faster, and being very honest with the doctors about how you are feeling and how your mediation is working on you."

From FGD 1: "Things like, you didn't take medicine, or things like you know you still struggle with delusion or hearing voice. But you know that there are people there to help. And that is when you know that you are able to face recovery, with a bolder heart. It gives you that courage to be able to help you face the challenges in life."

Continuing to take medications was, however, perceived by a small number of participants as a constant reminder that they were "not normal" and that they could never fully

recover. Not being on medications was mentioned during the FGDs and perceived as a benchmark for recovery by some participants. To them, taking "no medication" and having "no relapse" were key factors in recovery.

From FGD 6: "I have a problem with medication to be honest. Because I think when you are made to take medication like, there's this constant reminder like for me I'm still on medication and I'm technically supposed to be taking it every night but I kind of do it alternate night because I don't feel like I actually need it."

However, a participant proposed there was need to look beyond medication and focus on their personal meaning of recovery.

From FGD 1: "You can continue [to] go for treatment but you might not end up on the recovery journey. So it's very important to really make and create your own meaning of recovery, what is recovery to you and see how much and where are the treatment that really helps in your recovery journey because [for] some people [it] could be medicine but some people could be both medicine and probably psychotherapy and probably seeking other professional help. So I think that's when learning about yourself is also very important."

In this vein, almost all the participants shared how they took control of their own situations while encountering ups and downs, including behaviour modifications and self-appraisal. Many reported adapting their approach and expectations by setting goals for themselves yet at the same time going slow, pacing their studies and work, being open to whatever comes their way, choosing how to react and being strong, patient and positive. In terms of sustaining a healthy outlook while recovering, participants reported keeping themselves active, positive and calm, expressing themselves, confiding in others, doing new things and "going outside".

From FGD 3: "I'm doing things one step at a time, that means to monitor the secondary anxiety and to go through the resilience model. And if I get to go for the cert[ificate] in peer support right, I will enter it. Then after that, if not, then I will apply to be a social worker, one step at a time" and "I also learn that you cannot really change other people, or maybe what they say or what they think. But you can like try to change yourself, like you cannot find this sympathy or acceptance from someone else, or may be this is something you can give yourself."

From FGD 1: "It's like what you all say, like exercise, positivity. But I feel that it is not something that we can do every day. Like you can't just be happy and positive. There are times that you will feel vulnerable and we will cry. And there are times that we will face things like, we might have another episode of relapse. But the most important thing is to know that there are people there for you. And it is okay and it's alright to be vulnerable and honest and be open to them."

Despite these positive developments, some expressed residual reservations about being able to fully accept their illness and being symptom-free. The possibility of a relapse was also something that weighed on most of the participants' minds, and they expressed that it was something they were always mindful of and felt vulnerable about.

From FGD 6: "But now also like what [FGD participant] says, that yeah, it's about careful of not being in the relapse again. Must gauge your emotional stableness, is it stable, if not stable, must see doctor yeah."

From FGD 1: "It's like a process. So it's a continual process. Because sometimes when life shows you a difficulty, then you might go down. But you just need to learn to bounce back. So to say completely recovered; because anything can happen, you don't know relapse in the future might happen. Especially when you are going through a hard time."

Three: Facilitators of Recovery

Participants expressed several facilitators to their recovery that acted and overlapped at various stages in their recovery process or journey. The secondary themes that emerged were: personal agency, social and emotional support, treatments and services, faith and spirituality and other resources.

Personal Agency

Personal agency referred to the role the individual played in their own recovery, in terms of both the active steps participants might take or the characteristics participants might adopt that facilitate recovery. This included taking active ownership over one's physical and psychological health by taking up activities like sport and exercise and any recreational activities that one might enjoy and find relaxation in, as well as eating healthy and getting sufficient sleep. Additionally, being disciplined in taking one's medications on time and having awareness of the effects of medications on the self were also highlighted. Participants also strongly advocated the need to have a positive and optimistic perspective on life and its challenges, as well as being resilient and independent. Additionally, the social aspect of going out and engaging with others (even if initially distressing) and communicating personal problems with people that they trusted were also deemed as taking personal agency over their recovery.

Lastly, taking steps to gain knowledge and awareness over one's condition, experiences and emotions were raised as important in enabling participants to make important decisions over their well-being and their illness management. This might be through researching on one's condition or journalling one's thoughts and emotions.

From FGD 3: "I think it's also need to like, try to gauge my own like, my emotions la. Maybe if like, if you are unhappy, some people will be like, it's normal la life you cannot always be happy but then I like learn how to gauge if I'm really under a lot of stress and maybe if I'm very unhappy. I try to regulate it la, I won't treat it as nothing. I'll be like oh, I'll be more conscious about it."

From FGD 6: "So it's so important for everyone I think to be empowered with the ability to research and to find out and to be equipped with knowledge so that you know you can make better decisions with regards to how you want to further your recovery process, so I think that's one."

Social and Emotional Support

Social and emotional support came up strongly in its role in facilitating recovery among the participants. The physical support of loved ones such as family and friends being there during times when the participants were feeling down or admitted to the hospital was raised as being helpful in providing hope and courage to the participants in their recovery. Additionally, having an understanding of the illness from family and friends was also deemed important so that it allows them to be alert to any signs of impending relapses and thus getting the appropriate help.

Alternatively, this understanding might just allow them to empathise with the participants. These loved ones might then be inclined to help in regulating any distressing emotions of the participants that are associated with the challenges of daily life through simple advice and encouragement.

From FGD 2: "After [hospital admission] erm, I think it is a, it's a good thing that they (parents) were very patient with me, and they really listen to the doctor and like erm I mean like they, they know that it's part of my condition and they know how to handle it because like I will get very moody and then I get very emotionally then erm, then I was very irritable also and then erm … yeah they were be basically very patient with me la then they just erm reassure me that there will be a better every day."

From FGD 6: "When I'm working, when I'm stressed or whatever, when my boss see me as stressed, they will tell me to rest. That helps a lot. That's why it doesn't affect me but it helps me a lot because when they have learnt and accept, it become a helpful term for you instead of an affecting point."

Treatments and Services

This theme encompassed medical and psychosocial management by healthcare providers that facilitated their recovery. Participants acknowledged the role played by their psychiatrists and case managers in their recovery where they talked about the trust they had in their psychiatrists as an expert who knew best about the efficacy of medications while the case manager was described as someone who helped them navigate the health system as well as supported their education and workplace needs.

From FGD 3: "And my psychiatrist actually told me it's perfectly okay to live your life as normal and when I was making decision on whether I should choose like the more competitive schools or I should downgrade and choose the less competitive schools because of my current situation, he encouraged me to just go for whatever choice that I would think I am fit for without thinking I have this diagnosis."

Participants also talked about the role of medications, therapy and counselling in their recovery. While medications provided control over their symptoms, therapy was seen as helping them understand themselves better, cope with emotions and problems in a positive manner and counselling gave them an opportunity to express themselves without being judged. Meditation, relaxation techniques and mindfulness were also stated to contribute to recovery. Psychosocial interventions comprising structured and unstructured activities played a significant role in participants' recovery.

From FGD 1: "I think psychotherapy helped me in learning how to embrace and accept myself, not just in my symptoms but with regards to other issues also."

Carrying out these activities successfully instilled a sense of confidence in the patients and gave them a space where they could meet people from their own age groups and with similar interests who became part of their social circle and support. The activities indirectly helped them understand that they were not alone in the journey and there was a community they could tap on to learn from as well as contribute to. This created a recovery culture and instilled a sense of hope through the success of their peers as well as understanding that even renowned people suffer from schizophrenia.

From FGD 4: "But it helps what because it create[s] an ecosystem, a recovery culture whereby people with same similar experience can come together and support each other" and "To see the art work, showcase, exhibition by someone who has … the artist actually has schizophrenia herself, a Japanese artist XYZ."

Faith and Spirituality

While not brought up by a significant majority, faith in God and spirituality were raised as important contributors to recovery of the participants. Some participants felt that a belief in a God assured them that they were not alone when battling their mental condition, while also allowing them to be more accepting to things that have happened and inspiring hope for the future. Additionally, praying or meditating and seeking help from religious leaders were mentioned to help in alleviating personal anxieties and gaining clarity over their experiences.

From FGD 7: "Religious spiritual component is helpful la. I believe it's … it's what is it … it's making you be more calmer, and err be more err receptive or accepting of things that happened. Because some people believe that … believe in God, so they believe that it's a course, it's a life process, so they have to be accepting of the process that control them, that control in life la."

Other Resources

This theme included references, support received from peers, as well as open communication with them about their struggles and strengths. Participants mainly talked about how sharing their own story, owning their story and hearing about other people's stories of survival enabled their recovery. This theme emphasised the importance of both support groups and peer support groups in recovery. Participants felt that hearing about the experiences of others helped them feel that they were not alone in their journey. Sharing their stories reaffirmed their recovery and reminded them of their strengths.

From FGD 3: "To know, to hear about other persons who are in the recovery stage also, to know about that has helped me. Because I can see that I'm in some sense not alone, that there are other people going through the same thing, so it has helped me."

From FGD 7: "Sometimes when you share your story, it's like owning your story. And when you say that I've been through this, and I've overcome that, and being able to say them out, is like living it all over again. Yah. Like reinforcing the positive attributes of yourself, when you are sharing la."

Four: Concept Map

Based on the content of the FGDs, a broad concept map was developed to visualise the perspectives on recovery and understand how the various factors and components related to the secondary themes in the 3 main themes. Figure 2 illustrates the key observations. Based on the narratives of the participants, various facilitators belonging to 5 broad themes were interspersed with layers of their recovery journey while only 3 were mentioned in conjunction with the trauma layer; all 5 themes came up during the next 2 layers.

In summary, individuals reported deriving the meaning(s) of recovery only after they had accepted their condition. At the beginning of their journey when they were in turmoil, they had not even thought about, let alone defined, what recovery meant to them. The only facilitators reported to have helped advance their journey were faith, treatment(s) and emotional and social support. As they progressed through the ups and downs in their journey, the other enablers and personal agency were mentioned. Upon experiencing the various layers of their personal journey, participants reported emerging with 4 broad meanings on recovery from psychosis (Fig. 2).

Discussion

Schizophrenia and related psychoses are considered chronic mental conditions with fewer instances of complete remission. The diversity of psychiatric symptoms experienced during an episode such as hallucinations, delusions, paranoia and/or withdrawal are often accompanied with fluctuations in mood and anxiety which pose several challenges to the individuals' functioning and recovery. To further compound the impact, these illnesses often affect individuals at their most productive and formative years by disrupting educational, occupational and social progression.[22] Lately, research in the field of psychosis has delved beyond treatment effectiveness and clinical outcomes to identify facets of mental health-related stigma[23,24] and personal recovery perceived by individuals with psychoses.[9,25–8] Seeking understanding into recovery as defined by the individuals and exploring ways to foster it can enhance client-centeredness, improve outcomes and provide a structure to plan new and appropriate clinical approaches.[9] However, this is an emerging area of research. Much of the available information has been derived from Western populations where there is a more open dialogue on mental health. This study obtained insights into the concept of recovery as perceived in a non-Western society and in individuals who are in the early years from their diagnosis and who are still recovering. To the best of our knowledge, this is the first study to explore perceptions on recovery in multiethnic Asians who have experienced their initial episode(s) of psychosis.

The study identified 3 main themes related to perceptions around recovery in psychosis. For each theme, secondary themes were synthesised which were of relevance from the perspectives of individuals with psychosis. The themes identified in this study showed a number of similarities

with literature from qualitative investigations carried out elsewhere. A review conducted on qualitative studies in service users with psychosis identified 3 themes—recovery journey, facilitators and barriers to recovery.[27] The recovery journey as identified from the review started at a point preceding the episode of psychosis where users described their prior self. The rest of the journey was almost identical, albeit with some variations. The phase of turmoil reported by our study participants centred around expressions of a time they felt severe emotional chaos. However, the review also found that participants often expressed how they were trying to make sense of their experience which was not described by our participants. Likewise, the emphasis on "learning from the episode of psychosis" identified in the review in relation to our second theme on integration was not expressed by our participants. The experiences in the last phase of the journey—rebuilding—were, however, replicated in our study. Another conceptual framework of personal recovery from mental illness derived from a systematic review and expert consensus[9] identified 3 components that comprised 13 characteristics of the recovery journey, 5 processes of recovery and descriptions of recovery stages where the authors delinked journey from stages of recovery. While they listed the attributes of the journey such as being a process that is also a struggle and multidimensional in its nature, the chronological steps of recovery were mapped into a theoretical model of change starting with "pre-contemplation" and ending with "maintenance and growth".[9] There were, however, several common themes between this review and our study. Regardless of the differences in classifications and nomenclature, the take-home is that the recovery journey is often long, variable and complex. Hence, it is crucial that clinicians assess the phase individuals with psychosis are at and the unique challenges and situations that surround them to plan appropriate support and treatment for their clients' personal recovery.

Another important perspective is the emphasis on taking ownership of one's life, personal agency, self-acceptance and self-appraisal that was strongly expressed by our study participants. Personal agency was also identified as a recovery facilitator by Wood and Alsawy.[27] In their phenomenological investigation of young people with FEP to explore how subjective factors in the first stage of recovery impacted treatment outcomes, Connell et al[26] reported 2 superordinate themes that related to "self-estrangement and self-consolidation" and "making sense after traumatic events". Their findings were also based on the dialogical approach of Lysaker and Lysaker's[29] which proposed that an enriched sense of self can improve personal recovery from psychosis. Strauss[30] highlights that "how a person thinks, talks and reflects" can determine "their capacity to adjust and resume a normal developmental pathway". Hence, it is necessary to develop and equip individuals with the tools to manage their conditions.

It should be noted that the process of eliciting experiences from participants' narratives in FGDs resulted in several themes that overlapped with each other. Similar results were found in other qualitative studies where the themes intertwined "on a continuum" and were repeated multiple times in participants' narratives. However, the context of the content determined their position in the coding framework. In this study, the concepts of "acceptance" and "personal agency" were repeated across the 3 main themes. While recovery meant being able to accept themselves and their condition as reported by the participants, it also emerged as a key turning point in the journey towards recovery as well as a facilitator of "personal agency". Likewise, "personal agency" was repeated under meaning of recovery in the form of "Taking ownership of one's life" and served as a major facilitator in the reconstruction phase of the journey. Repetition of secondary themes in >1 superordinate or main theme is accepted in qualitative research. In instances of "concordant themes" that are closely inter-related, a concept map is often derived to understand the intricacies of these linkages.[21,31] We developed a simple concept map based on the secondary themes following content analysis (Fig. 2). This exercise helped in an understanding of how efforts can be focused in view of the personal recovery of individuals with psychosis.

It is evident from our schematic map and available literature that participants report having very little understanding or resources on recovery during the early episodes of psychosis.[9] This is a critical time in the period of individuals, particularly those who are experiencing psychosis for the first time. Appropriate support from professionals, treatment and, more importantly, family were described as being helpful during this period when participants were struggling with the trauma and had low personal capacity. It is therefore worthwhile to develop and empower external resources including the family of individuals with FEP. This inference resonates in research conducted elsewhere among caregivers of service users that highlights the collective responsibility of all stakeholders to address the unmet mental health needs of individuals.[33,34] A study from Australia had identified the needs of carers of people with psychosis as those that related to greater involvement of family in treatment

plans, information sharing and transparency, support for the carers and choice of care.[35] Likewise, a study of professional carers highlighted several challenges faced by them in adopting recovery-oriented approaches in mental health that were related to training, ownership and shared responsibility.[36] This study highlights the significance of understanding and enhancing external support for individuals with psychoses when they are unable to assist themselves, and this could serve as an important area for future research.

This study also indicates possible cultural influence on recovery perceptions in Asian populations. Drawing upon strengths from faith and social and emotional support from family were regarded as important to the recovery process by our study participants. Minority ethnic populations in Western societies were previously found to emphasise stigma and spirituality and were identified as culture-specific notions in recovery.[9] Our study supplements this literature. Additionally, our study highlighted the relevance of family and social support that is a hallmark of collectivist societies. Our results are in line with a recent article that explored cultural diversity in mental health.[37] Gopalkrishnan[37] emphasises the impact of social norms on mental health policy and practice and reports 5 key components that vary in Asian cultures—emotional expression of symptoms, shame, power distance between health professionals and users, collectivism and social support and influence of spirituality and religion. Our findings reflect some of these factors and help in understanding the notion of recovery in Asian settings.

The study provides understanding on some key aspects of recovery in psychosis; however, it has some limitations. Individuals included in this study were receiving treatment with an early psychosis intervention that used a structured approach to case management and treatment. There was also an emphasis on client empowerment whereby case managers introduced ways and opportunities to regain functioning and productivity. A number of secondary themes identified individual capacity and drive to achieve recovery targets. It is possible that some of the content may be a result of the training imparted during psychosocial activities conducted by EPIP which uses a risk reduction approach for its clients.[38] Most of the participants had a history of psychoses of <2 years and were under more intensive case management interventions. Moreover, given that this study included current clients of EPIP who were well enough to provide consent and were comfortable with describing their personal experiences in a group, the perspectives obtained in this study may relate more to stable clients than individuals with a longer duration of illness and treatment defaulters who are no longer under the purview of EPIP. The study also did not explore, in detail, how the personal goals of individuals had changed since their illness and how that might have affected what they perceived as their recovery. Additionally, the scope of the study was restricted to clients' perspectives; consequently, the experiences of those who were engaged in their care and treatment, such as informal and formal caregivers, were not included in the analysis.

Conclusion

This study presents clients' perspectives on recovery in psychosis. The emergent themes provide understanding into what recovery means to them, their experiences as they proceed with their recovery journey and factors they find helpful in this journey. The significance of acceptance and personal role in the recovery process is highlighted in the narratives of clients with psychoses. The study also indicates a need to incorporate recovery-relevant approaches as early as during the first episode of psychosis by engaging carers. Given that this study obtained perspectives of only 1 key stakeholder group—the clients—it would be useful to explore perceptions of recovery by family and professionals for comparison and to develop a comprehensive map of the recovery trajectory.

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REFERENCES

1. Chow WS, Priebe S. Understanding psychiatric institutionalization: a conceptual review. BMC Psychiatry 2013;13:169.
2. Gronfein W. Psychotropic drugs and the origins of deinstitutionalization. Soc Probl 1985;32:437–54.
3. Deegan PE. Recovery: the lived experience of rehabilitation. Psychosoc Rehabil J 1988;11:11–9.
4. Jacob KS. Recovery model of mental illness: a complementary approach to psychiatric care. Indian J Psychol Med 2015;37:117–9.
5. Davidson L, O'Connell MJ, Tondora J, Lawless M, Evans AC. Recovery in serious mental illness: a new wine or just a new bottle? Prof Psychol Res Pract 2005;36:480–7.
6. Ramon S, Healy B, Renouf N. Recovery from mental illness as an emergent concept and practice in Australia and the UK. Int J Soc Psychiatry 2007;53:108–22.
7. Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry 2005;162:441–9.

8. Silverstein SM, Bellack AS. A scientific agenda for the concept of recovery as it applies to schizophrenia. Clin Psychol Rev 2008; 28:1108–24.
9. Leamy M, Bird V, Boutillier CL, Williams J, Slade M. Conceptual framework for personal recovery in mental health: systematic review and narrative synthesis. Br J Psychiatry 2011;199:445–52.
10. Anthony WA. Recovery from mental illness: the guiding vision of the mental health service system in the 1990s. Psychosoc Rehabil J 1993;16:11–23.
11. Windell D, Norman R, Malla AK. The personal meaning of recovery among individuals treated for a first episode of psychosis. Psychiatr Serv 2012;63:548–53.
12. Windell DL, Norman R, Lal S, Malla A. Subjective experiences of illness recovery in individuals treated for first-episode psychosis. Soc Psychiatry Psychiatr Epidemiol 2015;50:1069–77.
13. Pitt L, Kilbride M, Nothard S, Welford M, Morrison AP. Researching recovery from psychosis: a user-led project. Psychiatr Bull 2007;31:55–60.
14. Davidson L, Borg M, Marin I, Topor A, Mezzina R, Sells D. Processes of recovery in serious mental illness: findings from a multinational study. Am J Psychiatr Rehabil 2005;8:177–201.
15. Law H, Morrison AP. Recovery in psychosis: a delphi study with experts by experience. Schizophr Bull 2014;40:1347–55.
16. Lam MML, Pearson V, Ng RMK, Chiu CPY, Law CW, Chen EYH. What does recovery from psychosis mean? Perceptions of young first-episode patients. Int J Soc Psychiatry 2011;57:580–7.
17. Verma S, Poon LY, Subramaniam M, Abdin E, Chong SA. The Singapore Early Psychosis Intervention Programme (EPIP): a programme evaluation. Asian J Psychiatry 2012;5:63–7.
18. Choo CC, Chew PKH, Ho CS, Ho RC. Prediction of quality of life in Asian patients with schizophrenia: a cross-sectional pilot study. Front Psychiatry 2017;8:198.
19. Guest G, Namey E, McKenna K. How many focus groups are enough? Building an evidence base for nonprobability sample sizes. Field Methods 2017;29:3–22.
20. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77–101.
21. MacQueen KM, McLellan E, Kay K, Milstein B. Codebook development for team-based qualitative analysis. CAM J 1998;10:31–6.
22. Liberman RP, Kopelowicz A, Ventura J, Gutkind D. Operational criteria and factors related to recovery from schizophrenia. Int Rev Psychiatry 2002;14:256–72.
23. Zhang Z, Sun K, Jatchavala C, Koh J, Chia Y, Bose J, et al. Overview of stigma against psychiatric illnesses and advancements of anti-stigma activities in six Asian societies. Int J Environ Res Public Health 2019;17:E280.
24. Subramaniam M, Abdin E, Picco L, Shahwan S, Jeyagurunathan A, Vaingankar JA, et al. Continuum beliefs and stigmatising beliefs about mental illness: results from an Asian community survey. BMJ Open 2017;7:e014993.
25. Gilburt H, Slade M, Bird V, Oduola S, Craig TKJ. Promoting recovery-oriented practice in mental health services: a quasi-experimental mixed-methods study. BMC Psychiatry 2013;13:167.
26. Connell M, Schweitzer R, King R. Recovery from first-episode psychosis and recovering self: a qualitative study. Psychiatr Rehabil J 2015;38:359–64.
27. Wood L, Alsawy S. Recovery in psychosis from a service user perspective: a systematic review and thematic synthesis of current qualitative evidence. Community Ment Health J 2018;54:793–804.
28. Lim MW, Remington G, Lee J. Personal recovery in serious mental illness: making sense of the concept. Ann Acad Med Singapore 2017;46:29–31.
29. Lysaker PH, Lysaker JT. Schizophrenia and alterations in self-experience: a comparison of 6 perspectives. Schizophr Bull 2010;36:331–40.
30. Strauss JS. Subjective experiences of schizophrenia: toward a new dynamic psychiatry–II. Schizophr Bull 1989;15:179–87.
31. Armborst A. Thematic proximity in content analysis. SAGE Open 2017;7:2158244017707797.
32. Wheeldon J, Faubert J. Framing experience: concept maps, mind maps, and data collection in qualitative research. Int J Qual Methods 2009;8:68–83.
33. Pope MA, Jordan G, Venkataraman S, Malla AK, Iyer SN. "Everyone has a role": perspectives of service users with first-episode psychosis, family caregivers, treatment providers, and policymakers on responsibility for supporting individuals with mental health problems. Qual Health Res 2019;29:1299–312.
34. Wainwright LD, Glentworth D, Haddock G, Bentley R, Lobban F. What do relatives experience when supporting someone in early psychosis? Psychol Psychother 2015;88:105–19.
35. Poon AWC, Joubert L, Harvey C. Perceived needs of carers of people with psychosis: an Australian longitudinal population-based study of caregivers of people with psychotic disorders. Health Soc Care Community 2018;26:412–22.
36. Williams A, Fossey E, Farhall J, Foley F, Thomas N. Recovery after psychosis: qualitative study of service user experiences of lived experience videos on a recovery-oriented website. JMIR Ment Health 2018;5:e37.
37. Gopalkrishnan N. Cultural diversity and mental health: considerations for policy and practice. Front Public Health 2018;6:179.
38. Chong SA, Lee C, Bird L, Verma S. A risk reduction approach for schizophrenia: the Early Psychosis Intervention Programme. Ann Acad Med Singapore 2004;33:630–5.

Review Article

Extracorporeal Membrane Oxygenation for Severe Respiratory Failure During Respiratory Epidemics and Pandemics: A Narrative Review

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Abstract

Introduction: Epidemics and pandemics from zoonotic respiratory viruses, such as the 2019 novel coronavirus, can lead to significant global intensive care burden as patients progress to acute respiratory distress syndrome (ARDS). A subset of these patients develops refractory hypoxaemia despite maximal conventional mechanical ventilation and require extracorporeal membrane oxygenation (ECMO). This review focuses on considerations for ventilatory strategies, infection control and patient selection related to ECMO for ARDS in a pandemic. We also summarise the experiences with ECMO in previous respiratory pandemics. Materials and Methods: A review of pertinent studies was conducted via a search using MEDLINE, EMBASE and Google Scholar. References of articles were also examined to identify other relevant publications. Results: Since the H1N1 Influenza pandemic in 2009, the use of ECMO for ARDS continues to grow despite limitations in evidence for survival benefit. There is emerging evidence to suggest that lung protective ventilation for ARDS can be further optimised while receiving ECMO so as to minimise ventilator-induced lung injury and subsequent contributions to multi-organ failure. Efforts to improve outcomes should also encompass appropriate infection control measures to reduce co-infections and prevent nosocomial transmission of novel respiratory viruses. Patient selection for ECMO in a pandemic can be challenging. We discuss important ethical considerations and predictive scoring systems that may assist clinical decision-making to optimise resource allocation. Conclusion: The role of ECMO in managing ARDS during respiratory pandemics continues to grow. This is supported by efforts to redefine optimal ventilatory strategies, reinforce infection control measures and enhance patient selection.

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Key words: Acute Respiratory Distress Syndrome, Coronavirus disease 2019, ECMO, Infection control, Mechanical ventilation

Introduction

Respiratory viruses resulting in epidemics and pandemics such as the severe acute respiratory syndrome coronavirus (SARS), H1N1 influenza A (H1N1pdm09), Middle East respiratory syndrome coronavirus (MERS-CoV) and the recent novel coronavirus disease 2019 (COVID-19) can lead to severe acute respiratory failure (ARF) that requires intensive care support. In a subset (4–40%) of patients with severe ARF (such as severe acute respiratory distress syndrome [ARDS]) refractory to maximal conventional mechanical ventilation (MV) support, extracorporeal membrane oxygenation (ECMO) may be required.[1,2] Briefly, ECMO uses modified cardiopulmonary bypass technology to provide respiratory or cardio-respiratory support in potentially reversible conditions where maximal conventional intensive care support is failing (Fig. 1). It is broadly categorised into venovenous (VV) and venoarterial (VA) ECMO. In VV ECMO, blood is drained from the venous system, pumped into an artificial lung for addition of oxygen and removal of carbon dioxide, before being returned to a central vein, thus providing respiratory support. In VA ECMO,

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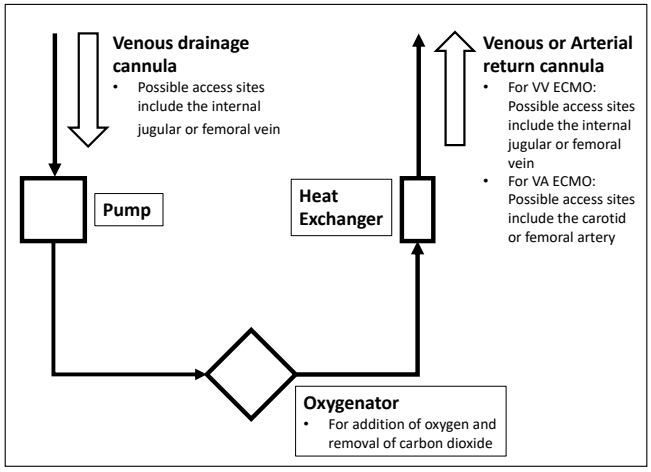

Fig. 1. Schematic representation of an ECMO circuit. Deoxygenated blood is drained from a central vein and pumped to a membrane lung oxygenator, where oxygen is added and carbon dioxide is removed. The oxygenated and decarboxylated blood is passed through a heat exchanger before being returned to the patient, with the site of the return cannulae varying according to the mode of ECMO. Blood in the extracorporeal circuit cools to room temperature and a heat exchanger is necessary for thermoregulation.
ECMO: Extracorporeal membrane oxygenation; VA: Venoarterial; VV: Venovenous

blood is drained from the venous system, pumped into an artificial lung and returned to the aorta or femoral artery, thus providing cardio-respiratory support. Although the evidence for ECMO in ARDS is limited, ECMO remains included in major clinical practice guideline recommendations for management of patients with severe ARDS.

In initial reports of the COVID-19-infected pneumonia epidemic, up to 25% of patients were critically ill, with significant mortality ranging between 10–60% within this group.[3–5] Among patients that required care in the intensive care unit (ICU), ARDS was the most common reason for admission (61–67%) and 8–15% of these patients required ECMO support.[3–5] As such, a review of the use of ECMO during respiratory epidemics and pandemics is timely. In this narrative review, we focus on some pertinent considerations in the use of ECMO during epidemics and pandemics (such as ventilatory strategies during ECMO and infection control considerations). We summarise the experience of the use of ECMO in patients with SARS, H1N1pdm09, MERS-CoV and‒COVID-19 with the main aim to outline potential lessons learnt and applications for ECMO deployment for the current COVID-19 and future epidemics/pandemics. For clinical aspects that we did not include, we refer readers to other excellent review articles on the use of ECMO in the ICU.[6,7]

For the purpose of this narrative review, we searched MEDLINE, EMBASE and Google Scholar using the following MESH terms and keywords: ECMO, epidemics, pandemics, SARS, H1N1pdm09, MERS-CoV and COVID-19. Additionally, we examined the references of articles found and included those that we considered appropriate for this focused narrative review.

Ventilatory Strategies During ECMO

MV is life-saving for patients with severe ARF. However, MV results in repetitive stress and strain on diseased lung units with consequent distortion of lung parenchyma and extracellular matrix, leading to ventilator induced lung injury (VILI).[8] The 2 key contributory mechanisms in VILI are repetitive volutrauma (from excessive tidal volumes), and atelectrauma (from repetitive opening and closure of alveoli).[8] Lung protective ventilation (LPV) techniques are recommended for both adults[9] and children[10] with the aim to achieve a delicate balance of adequate alveolar recruitment of non-aerated and injured lung segments while limiting over-distension.

Key determinants of VILI which can be manipulated during MV include tidal volume (TV), positive end expiratory pressure (PEEP), plateau pressure (Pplat) and driving pressure (ΔP). Additionally, increased work of breathing and patient-ventilator dyssynchrony contribute to increases in transpulmonary pressures and lung injury and may be mitigated with sedation and neuromuscular blockade.[11] However, the relative contributions of disease, ventilator and patient factors to the development of VILI and the optimal manipulation of these factors to minimise VILI remains unknown.[8]

In adults, conventional MV with low TV (≤6 mL/kg) is guided by a landmark study which showed a significant reduction in 28-day mortality in adults with ARDS in the patient group that was ventilated with TV ≤6 mL/kg compared to 12 mL/kg.[9] This has since been widely accepted and incorporated into guidelines for the management of ARDS.[12] However, the caveat is that LPV strategies with low TV and airway pressures may result in significant respiratory acidosis. In patients with severe ARDS, this may necessitate the use of high respiratory rates which in turn is hypothesised to contribute to VILI.[13] Thus, there is growing interest and evidence for the use of LPV in conjunction with extracorporeal life support (ECLS) such as VV ECMO or extracorporeal carbon dioxide removal ($ECCO_2R$) to achieve adequate oxygenation and carbon dioxide clearance while implementing lung rest and mitigating VILI.

Although early use of ECMO has not been conclusively shown to be superior to ECMO initiated as rescue therapy,[14] the possibility that it may facilitate mitigating VILI and resultant morbidity and mortality remains of heightened

Table 1. Summary of Mechanical Ventilation Guidelines for ARDS with and without ECLS and Paediatric ARDS

Variable	ARDS	PARDS	During ECLS for ARDS
Recommending body/landmark trials	ATS/ESICM/SCCM[*] ARDSNet[†] PROSEVA[‡] ART[§]	PALICC[¶]	ECMONet[**] EOLIA[††]
Tidal volume	4 – 8 mL/kg	Poor lung compliance: 3 – 6 mL/kg Good lung compliance: 5 – 8 mL/kg	Adjusted to goal Pplat; typically ≤4 mL/kg PBW
PEEP	Higher PEEP with moderate to severe ARDS[‖]	10 – 15 cmH_2O; allowance of ≥15 cmH_2O in severe PARDS	≥10 cmH_2O
Pplat	≤30 cmH_2O	-	≤24 cmH_2O
DP	-	-	≤14 cmH_2O
RR	-	-	≤10 breaths/min
PIP	-	≤28 cmH_2O (≤32 cmH_2O when there is stiff chest wall)	-
Arterial blood gas parameters	-	Allow permissive hypercarbia (pH 7.15 – 7.30) when there are no contraindications[#]	PaO_2 65 – 90 mmHg $PaCO_2$ <45 mmHg
FiO_2	-	-	0.3 – 0.5
SpO_2	-	88 – 92% for severe PARDS	-
Prone positioning	>12 – 16 hr/day for severe ARDS	-	-
HFOV	Routine use in moderate or severe ARDS is discouraged	When Pplat ≥29 cmH_2O	-
Recruitment manoeuvres	Role is controversial	-	-
ECMO	No recommendation for or against	-	-

ΔP: Driving pressure; ARDS: Acute respiratory distress syndrome; ECLS: Extracorporeal life support; ECMO: Extracorporeal membrane oxygenation; FiO_2: Fraction of inspired oxygen; HFOV: High frequency oscillatory ventilation; $PaCO_2$: Partial pressure of arterial carbon dioxide; PaO_2: Partial pressure of arterial oxygen; PARDS: Paediatric acute respiratory distress syndrome; PBW: Predicted body weight; PEEP: Positive end-expiratory pressure, PIP: Peak inspiratory pressure; Pplat: Plateau pressure; RR: Respiratory rate; SpO_2: Peripheral capillary oxygen saturation

[*]Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;195:1253–63.

[†]Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301–8.

[‡]Guerin C, Reignier J, Richard J-C, Beuret P, Gacouin A, Boulain T, et al. PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159–68.

[§] Cavalcanti AB, Suzumura EA, Laranjeira LN, Paisani DM, Damiani LP, Guimaraes HP, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2017;318:1335–45.

[‖]Guidelines from the Surviving Sepsis Campaign[91] recommend higher PEEP for ARDS in coronavirus disease 2019 (COVID-19).

[¶]Jouvet P, Thomas NJ, Wilson DF, Erickson S, Khemani R, Zimmerman J, et al. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med 2015;16:428–39.

[#]Contraindications include raised intracranial pressure, severe pulmonary hypertension and certain congenital heart lesions.

[**]Abrams D, Schmidt M, Pham T, Beitler JR, Fan E, Golgher EC, et al. Mechanical ventilation for ARDS during extracorporeal life support: research and practice. Am J Respir Crit Care Med 2020;201:514–25.

[††]Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378:1965–75.

interest, particularly in those with severe ARDS. ECMO support can potentially fully replace the native lung function of gas exchange, allowing for reduction in TV, Pplat and ΔP.[15] Current recommendations for the use of low TV whilst supported on ECMO are based on the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial[14] (Table 1) which demonstrated an improvement in 60-day mortality in those randomised to early ECMO (35%) vs conventional MV with LPV (46%), although this did not reach statistical significance. The potential benefit of further minimising TV is supported by a study from the United States[16] which showed an inverse linear relationship between TV and mortality at two years with no apparent lower limit for the association. A porcine model of ARDS comparing non-protective, protective and near apnoeic ventilation (TV 2.1 mL/kg and respiratory rate of 5 breaths/minute) found the least amount of histological injury associated with the latter, supporting this hypothesis.[17] To test the extent of this benefit in patients supported on ECLS, 2 trials are currently ongoing to assess the role of ultra-low tidal volumes (up to 3 mL/kg) in conjunction with $ECCO_2R$, the SUPERNOVA[29] and REST[30] trials. Although on a different form of ECLS, the outcomes of these trials may be extrapolated to some extent to patients supported on ECMO. However, the benefits of minimising VILI with the use of LPV must be balanced with potential risks of adverse events related to ECLS and the availability of expertise to safely implant, monitor and manage it in addition to the cardiopulmonary interactions and physiological changes that may result from this approach.

There is good evidence for reduction in mortality with lower TV,[9] lower ΔP[20] and plateau pressures.[20,21] However, the role of optimal PEEP and recruitment manoeuvres are less clear and hence feature less prominently in practice guidelines. A database review of ECMO practices in France and Australia from 2007–2013 found an association between improved survival and higher PEEP (12–14 vs 10–12 cmH_2O) with slightly higher TV (4–6 vs 2–4 mL/kg) following ECMO initiation.[15] Hence current guidelines advocate for PEEP between 10–15 cmH_2O in patients with severe ARDS[10,12,14] (Table 1).

In adults, routine high frequency oscillatory ventilation (HFOV) use in severe ARDS is discouraged[12] following 2 large randomised controlled trials (RCTs) of HFOV in critically ill adults: one of which was stopped early[22] as the in-hospital mortality in the HFOV group was significantly higher than the control group (48% vs 35%, relative risk [RR] of death with HFOV, 1.33; 95% confidence interval [CI] 1.09–1.64; $P = 0.005$) and the other which showed no difference between the HFOV and conventional MV arms.[23] In contrast to adult guidelines, HFOV continues to be recommended in children and used as a rescue therapy in critically ill children with severe ARF as some studies suggest benefit while others raise concerns of harm.[10] An RCT comparing HFOV to conventional MV in 112 children with paediatric acute respiratory distress syndrome (PARDS) found a higher incidence of survivors in the HFOV group for children with severe PARDS with a baseline oxygenation index >16 (40% vs 15.8%; $P = 0.004$).[24] Conversely, a large observational study of children in Asia involving 118 pairs of patients matched using genetic matching method, found an association between HFOV and 28-day mortality in PARDS (odds ratio [OR] 2.3; 95% CI 1.3–4.4; $P = 0.01$).[25] While this raises some concerns about the safety of use of HFOV in children, the utility of HFOV in the paediatric ICU remains uncertain. Taking into consideration the data from both adult and paediatric patients, it remains unclear whether patients supported on ECMO should be supported on HFOV in an attempt to reduce VILI. However, the concurrent use of ECMO and HFOV may facilitate HFOV settings akin to LPV or near-apnoeic MV, which would be very different compared to the "rescue" settings that have been studied thus far. This may potentially be superior to LPV in mitigating atelectrauma and should be explored in future studies.

Most recommendations for MV in patients with severe ARDS with or without ECMO support comes from animal and adult studies and these may not extrapolate to children. In children, pressure targeted modes of MV are more frequently used than volume-controlled modes and peak inspiratory pressure (PIP) rather than TV seems to correlate with outcomes.[26,27] No specific range of TV has been shown to impact mortality in PARDS.[28] In a prospective observational multicentre study of the Australian and New Zealand Paediatric Intensive Care Society (ANZPICS) study group, higher TV was associated with reduced mortality even after adjusting for severity of lung disease. In that study, PIP > 25 cmH_2O was associated with increased odds of mortality of 10% (OR 1.1; 95% CI 1.020–1.199).[29] Similarly, in a retrospective review of children with ARF, TV was not associated with mortality and lower median PIP of 26 cmH_2O (interquartile range [IQR] 22–30) was observed in survivors compared with 30 cmH_2O (IQR 24–34, $P < 0.01$) in non-survivors.[27] In addition, a retrospective multicentre cohort of PARDS patients in Asia also showed increased ventilator free days in those supported with PIP ≤28 cmH_2O.[26]

In summary, there is increasing evidence to support the use of LPV in conjunction with ECLS to minimise VILI.

While not recommended routinely, ECMO or $ECCO_2R$ used in conjunction with LPV to manage respiratory acidosis and hypoxia to the extent of allowing near apnoeic ventilation holds promise in the management of severe ARF and a potential for significant reduction in VILI. While the principle of LPV in conjunction with ECMO should also apply for children, it is important to remain mindful that the evidence is extrapolated from adults and that there may be physiological differences when these are applied to children supported on ECMO.

Infection Control Considerations for the Patient on ECMO

The goals for infection control measures for the patient on ECMO support for ARF in the context of a respiratory pandemic are two-fold: 1) mitigation of the risk of co-infections for the patient and; 2) prevention of transmission of novel respiratory pathogens to healthcare workers. Adequate planning and preparation are essential to develop protocols for routine management and in times of crisis. Healthcare staff must also be trained to respond appropriately at various states of emergency. Staff knowledge and competence must be ensured, especially when they are required to function in a stressful, high-risk environment requiring complex and resource-intensive care.

In 2008, the Extracorporeal Life Support Organization (ELSO) created an Infectious Disease Task Force to address the issue of diagnosis, treatment and prevention of infections for ECMO patients. An analysis of the ELSO database reported that the risk of infection on ECMO increased with increasing patient age and with ECMO runs longer than 1–2 weeks.[30] The most common reported organisms include coagulase-negative staphylococci, Candida species, Pseudomonas and Staphylococcus aureus, with smaller numbers of gram-negative organisms such as Enterobacter, Klebsiella, Enterococcus and Escherichia coli species.[30] This should be considered when selecting empirical antibiotic therapy for suspected infections, with a lower threshold for initiating anti-fungal therapy given the high incidence and mortality associated with Candida sepsis.[31] Recommended infection control precautions for patients supported on ECMO include: 1) treating the ECMO circuit as a protected central line, so that "breaking" the line would be avoided as much as possible, with blood sampling preferentially taken from patient sites such as arterial catheters and medication administration through the circuit restricted to continuous infusions rather than intermittent doses; 2) measures to prevent ventilator associated pneumonia such as elevation of the head of the bed, medical treatment of gastroesophageal reflux, pulmonary toilet and oral or gastrointestinal decontamination protocols; 3) initiation of enteral nutrition where possible to maintain gut mucosa, prevent bacterial translocation and reduce the need for parenteral nutrition; 4) administration of parenteral nutrition through a dedicated central venous line rather than directly administering concentrated glucose to the ECMO circuit; 5) administration of blood products or intermittently dosed drugs via peripheral vascular access; 6) avoiding the insertion of new long term tunnelled or cuffed vascular access while on ECMO due the risk of haematoma formation and infection and; 7) removal of all unnecessary lines, tubes and devices once the patient is stable on ECMO.[32] These are summarised in Table 2.

The practice of "surveillance" periodic blood, urine or sputum cultures did not demonstrate benefit and was discouraged, with cultures recommended only if sufficient clinical suspicion arises.[32] However, patients on ECMO receive extracorporeal thermoregulation, with blood in the circuit naturally cooling down and heated to normothermia before returning to the body. This makes it difficult, but not impossible for a patient to mount a fever due to an infection. The extent of ECMO circuit flow should also be considered. Patients with relatively low ECMO flows have a smaller proportion of blood circulating extracorporeally and so can mount a fever, whereas patients with high ECMO flows are subject to a greater degree of extracorporeal thermoregulation and are less likely to generate fever. In such settings, careful clinical examination is required to evaluate for infections and any degree of febrile response while on ECMO should be considered significant. Generally, single dose or 24-hours of prophylactic antibiotic coverage is recommended upon ECMO cannulation, but data did not support longer durations of prophylaxis without specific culture or physiological evidence of ongoing infection or in the absence of risk factors such as transthoracic cannulation, immunocompromised states or pre-existing skin colonisation (such as multidrug resistant organisms or yeast).[30,32] There is a lack of consensus regarding the management of catheter-related infections. Exchanging a catheter at the same site over a guidewire is unlikely to be helpful, given the high likelihood of microbial colonisation of the tract.[33] However, efforts to remove a catheter and replacing it at a new site must be balanced with considerations for the antibiotic susceptibility of the infecting organism, the risk of significant haemorrhage and accessibility of vascular access.

Most respiratory viruses, including SARS, H1N1pdm09, MERS-CoV and COVID-19, are transmitted via respiratory droplets and direct contact with infectious secretions or contaminated fomites.[34,35] However, aerosol-generating

Table 2. Summary of Infection Control Recommendations While on ECMO*

Recommendation	Description
Circuit management	• Treat ECMO circuit as a protected central line to minimise unnecessary accessing or "breaking" of the circuit • Obtaining routine blood samples from patient sites such as arterial catheters rather than from the circuit • Use of needleless hubs for all connection, stopcocks and access sites in the circuit • Use of chlorhexidine preparation solution rather than alcohol • Only allow administration of continuous infusions via the circuit, but not intermittently dosed medications • Avoid pairing care of ECMO patients with other patients with multi-drug resistant organisms or with grossly contaminated wounds or serious infections • Frequent hand washing and easy access to cleansing solutions before handling the circuit
Prevention of systemic infections	• Measures to prevent ventilator-associated pneumonia such as elevation of the head of the bed, oral prophylaxis and medical treatment of gastro-oesophageal reflux • Appropriate pulmonary toilet, suctioning and bronchoscopy when indicated • Early tracheostomy in non-paediatric patients to improve pulmonary toilet, reduce potential for gastrointestinal contamination and reduce sedation requirements • Consider use of oral or gastrointestinal decontamination protocols • Consider early and complete enteral nutrition to maintain gut mucosa, prevent bacterial translocation and to help avoid the use of parenteral nutrition • When parenteral nutrition is necessary, administer it directly to patient via a clean dedicated line rather than expose the circuit to a high glucose concentration which increases risk of infection • Administration of intermittently dosed drugs or blood products via peripheral vascular access • Strict sterile technique when accessing central lines • Avoid insertion of new tunnelled or cuffed vascular catheters while on ECMO due to the risk of haematoma formation and subsequent infection • Removal of all unnecessary lines, tubes and devices once patient is stable on ECMO
Use of prophylactic antibiotics	• There is no data to support the routine use of prophylactic antibiotics for patients on ECMO without specific culture or physiologic evidence of ongoing infection • Single dose or 24-hour prophylactic antibiotic coverage for ECMO cannulation • Prophylactic antibiotics may be considered in patients with risk factors such as transthoracic cannulation, immunocompromised states or with pre-existing skin colonisation with multidrug resistant organisms or yeast • Prophylaxis for surgical procedures while on ECMO should follow standard guidelines • Use of anti-fungal prophylaxis in patients deemed to be at high risk of fungal infection

ECMO: Extracorporeal membrane oxygenation

*Extracorporeal Life Support Organization. Infectious Disease Task Force: Infection Control and Extracorporeal Life Support. Available at: https://www.elso.org/Portals/0/Files/Infection-Control-and-Extracorporeal-Life-Support.pdf. Accessed on 13 February 2020.

procedures within the ICU such as endotracheal intubation, extubation, airway suctioning, bronchoscopy and cardiopulmonary resuscitation may result in airborne transmission via small aerosol spread.[36] Thus, infection control measures for healthcare workers in contact with patients with novel respiratory pathogens in the ICU should include: 1) adequate personal protective equipment (PPE), including a gown, gloves, eye goggles or face shield and N95 respirator; 2) adequate hand hygiene; 3) environmental cleaning and disinfection; 4) measures aimed at containing patient secretions; and 5) dilution and removal of airborne contaminants.[37,38] These apply to any patient receiving MV and are summarised in Table 3.

Of the abovementioned infection control measures, containing patient secretions and removal of airborne contaminants are of particular importance given the nature of care required by patients supported by MV. Specific precautions are required to reduce aerosolisation, contain secretions and reduce duration of exposure to secretions. Endotracheal intubation should be considered early, to allow sufficient time for infection control preparations and be performed in a timely and controlled fashion by the most experienced personnel present, with the least number of assisting staff possible to limit exposure. In addition to other PPE, staff present for intubation (or any other aerosol-generating procedure) should be equipped with powered air-purifying respirators. The patient should be adequately sedated and paralysed to prevent coughing and agitation. If possible, bag-mask ventilation should be avoided and apnoeic oxygenation may be considered. If bag-mask ventilation is necessary, a 2-person technique should be used to ensure tight mask seal at the face and a high-efficiency particulate air (HEPA) filter may be fitted to reduce aerosolised pathogen load.[38] Cuffed endotracheal tubes should be employed to reduce airway leak. Regarding routine care of the ventilated patient, closed system (in-line) airway suctioning should be employed, with a HEPA filter connected to the ventilator expiratory port.[38] In order to reduce condensation within the ventilator tubing and the need to "break" the ventilator circuit to drain

Table 3. Summary of Infection Control Precautions in the Intensive Care Unit During a Respiratory Epidemic/Pandemic

Precaution	Description
Personal protective equipment	• Gown, gloves, eye goggles or face shield and N95 respirator • During aerosol-generating procedures, use powered air-purifying respirator • Provision of antechambers to patient rooms with visual instructions for donning and doffing, with spotter assistance • Sufficient containers for disposal of personal protective equipment, soiled linen and equipment that must be autoclaved
Hand hygiene	• Ensure easy access to alcohol-based hand rub and sinks with anti-bacterial soap and disposable towels inside and outside the patient room • Avoid touching face and environmental surfaces
Environmental cleaning and disinfection	• Trained personnel to clean and disinfect rooms with hospital-grade detergent/disinfectant • Clean frequently touched areas at least daily or once per shift
Containing patient secretions and reducing exposure	• Avoid aerosol-generating procedures if possible (such as bronchoscopy) • Limit the number of staff to essential personnel during aerosol-generating procedures • Consider early intubation by the most experienced personnel, in a timely and controlled manner, using a cuffed endotracheal tube with adequate sedation/paralysis and apnoeic oxygenation • Avoid bag-mask ventilation but if required, consider the 2-person technique to ensure tight mask seal with attached HEPA filter • Use closed system (in-line) airway suctioning • Attach HEPA filter to ventilator expiratory port • Attach HMEF to endotracheal tube • Avoid heated humidifier systems to reduce condensation within ventilator tubing • If ventilator circuit is disconnected, turn ventilator to standby mode with PEEP turned off • If high frequency oscillatory ventilation is required, consider maintaining inflated cuff for endotracheal tube, with HEPA filter and HMEF attached to circuit • Avoid nebulised medications if possible • The use of non-invasive ventilation is controversial and may pose additional nosocomial transmission risk
Dilution and removal of airborne contaminants	• Use of negative pressure isolation rooms • Installation of or provision of portable photocatalytic HEPA filters to reduce airborne pathogen load • Appropriate hospital design to augment ventilation within the ward • Open windows and keep fans running to encourage ventilation within the ward
Others	• Ensure adequate staff education and training • Limit visitors and personnel to those essential for patient care and support • Avoid patient movement/transportation unless absolutely necessary. If required, ensure appropriately trained and equipped transport and receiving teams, with shortest route of movement with minimal exposure to other personnel, measures taken to prevent dispersal of patient respiratory secretions and disinfection of route and destination. • Provision of frequently used equipment/resuscitation equipment in individual rooms

HEPA: High-efficiency particulate air; HMEF: Heat and moisture exchanging filter; PEEP: Positive end-expiratory pressure

water, heated humidifier systems should be removed and replaced with a heat and moisture exchanging filter (HMEF) at the endotracheal tube.[39] However, the medical team must be mindful of the increase in dead space and potential increase in airway resistance with HMEFs and HEPA filters, which may impact on the adequacy of MV and validity of capnography. Thus, the patients' respiratory effort, gas exchange and filter quality must be regularly monitored, with filters replaced when necessary. If end-tidal capnography traces are significantly affected, especially in severe ARF with significant intrapulmonary shunting, transcutaneous carbon dioxide monitoring is a potential alternative for real-time non-invasive carbon dioxide monitoring.[40] If disconnections in the ventilator circuit are required, the endotracheal tube should be clamped, with the ventilator transiently turned to standby mode and positive end-expiratory pressure stopped. The risks of nosocomial transmission of respiratory pathogens with HFOV remains uncertain. If HFOV is deemed clinically necessary for the patient, maintaining cuffed endotracheal tubes with the addition of HMEF and HEPA filters to the HFOV circuit may mitigate transmission risk.

Measures to dilute and remove airborne contaminants include strategies to improve ventilation within the ward and the use of photocatalytic HEPA filtration devices, which ideally should be incorporated in negative pressure isolation rooms. Several studies have linked reduced nosocomial transmission of SARS in hospitals to

augmented ventilation within the ward. In a Vietnamese hospital, there was no transmission of SARS in wards with large spacious rooms, high ceilings, large windows and continuously running ceiling fans.[41] Another hospital in China compared window surface area to room volume and found that rooms without windows had the highest nosocomial transmission rates, whereas rooms with larger window surface area to room volume ratios had the lowest transmission rates.[42] If not already available, addition of photocatalytic HEPA filter units to wards may be considered to remove and deactivate airborne pathogens.

ECMO Experience with the Severe Acute Respiratory Syndrome Coronavirus (SARS)

SARS was a novel coronavirus that first emerged as an outbreak of atypical pneumonia in Guangzhou Province, China, in late 2002.[37] It is phytogenetically diverged from other human coronaviruses and is more closely related to a group of lineage B betacoronaviruses found in civets and Chinese horse shoe bats.[43] Rapid progression to ARDS occurred in 20–25% of infected individuals with a mortality rate of approximately 10%.[44] To our knowledge, there were no reports of ECMO use during the SARS epidemic, likely due to lack of relevant expertise and infrequent use during that particular period.

ECMO experience with the H1N1 Influenza A Pandemic (H1N1pdm09)

Compared to prior epidemics, H1N1pdm09 tended to cause critical illness and mortality among a younger patient population.[1] Although the disease course was mostly mild and self-limiting, up to 20% of hospitalised patients were admitted to ICU, with 80% of these requiring MV.[1] Progression from pneumonia to ARDS was rapid, with a mean duration of 1 day from hospitalisation to ICU admission.[1,45]

The H1N1pdm09 pandemic played an important role in the expansion of ECMO as a rescue therapy in adult ICUs. Prior to 2009, ECMO was primarily utilised in the neonatal and paediatric population, with significant controversy regarding the application of ECMO for adults.[46] Most early data in adults showed poor outcomes, particularly for ARDS, and only a few institutions had established ECMO programs for adult ARF at that time.[46] In 2009, results from the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial demonstrated that patients who received ECMO for severe ARF had improved rates of disability-free survival compared to those who received conventional management (63% vs 47%; RR 0.69; 95% CI 0.05–0.97).[47] This was followed by a publication from the Australia New Zealand ECMO Influenza Investigators group that reported a 21% mortality rate among H1N1pdm09 patients who received ECMO in ICUs across Australia and New Zealand.[48] In comparison, overall mortality rates for ARDS on ECMO at the time were 37–48%[47] and mortality for severe H1N1pdm09 ARDS at institutions where ECMO was not available was 46%.[49] Taken collectively during that period, ECMO seemed to hold promise in the management of the pandemic.

The surge in rapidly progressive, severe ARDS in a generally young population due to H1N1pdm09, paired with promising results from these publications, spurred resurgence in exploring ECMO as a rescue therapy for adults with ARF. Although standard ECMO criteria in H1N1pdm09 was lacking, the CESAR trial was frequently referenced and refractory hypoxemia was the primary indication for cannulation. One-third of patients who required MV have been reported to be supported on ECMO for a duration of 10–18 days.[21,48] There was compelling evidence that while H1N1pdm09 can cause severe illness, the disease process was reversible and transfer to an ECMO centre was associated with improved mortality rates in H1N1pdm09 ARDS compared to non-transfer (24% vs 51%; RR 0.47; 95% CI 0.31–0.72).[50] Favourable H1N1pdm09 ECMO outcomes were associated with fewer days of pre-cannulation MV,[51] rapid wean of MV to low pressure settings once on ECMO support,[21] and early initiation of neuraminidase inhibitor treatment.[45] ECMO complications were largely haemorrhagic, thrombotic, or infectious.[48] Rates of intracranial bleeding were reported at 1–11%.[21,48,50,51]

During this pandemic, institutions with ECMO experience took measures to strengthen their programs to meet the anticipated surge in demand,[52] while others with limited or no prior experience sought to develop their own ECMO capabilities.[53] These efforts were met with varying success.[48] The ability for regional systems and individual institutions to adapt to the surge in demand during a crisis is critical to optimise patient outcomes. Factors that appear to have contributed to successful ECMO expansion during the 2009 pandemic include centralisation of ECMO within designated centres of excellence and interhospital transfer capabilities, the establishment of clear criteria for referral to ECMO centres and ECMO initiation, and a structured simulation-based training program to quickly equip ICUs with varying prior ECMO experience to meet anticipated demand.[51]

ECMO Experience with the Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

MERS-CoV was first described in 2012 in the Middle East and is caused by a novel zoonotic coronavirus postulated to be transmitted from dromedary camels.[54] Mortality in infected individuals is high (35%),[55] likely as a result of virus virulence and lack of definitive therapies. Indeed, the most common complication is that of ARDS. In addition to the hallmark of refractory hypoxemia, patients who progressed to ARDS were prone to multiorgan failure and septic shock,[56] often prompting the need for escalation to ECMO as rescue therapy. For ethical concerns, no RCT has been conducted to assess efficacy of ECMO in this cohort of patients. The use of ECMO in MERS-CoV is also limited due to the presence of contraindicated comorbidities, compounded by a lack of resources and trained personnel especially in rural areas.[54] Median time from symptom onset to invasive ventilation and/or ECMO initiation ranged from 4.5 to 7 days[57] which is earlier than that reported in SARS.[42] Guery et al described the clinical course of 2 adults who required ECMO for MERS-CoV for refractory ARF.[58] Bronchoalveolar lavage samples of both patients showed extremely high viral loads and at time of publication, the index patient had demised while the other one remained on ECMO. A retrospective cohort study (n = 35) performed in Saudi Arabia compared MERS-CoV infected patients who fulfilled ECMO criteria (as defined by the ELSO guidelines) but did not receive ECMO (due to lack of an ECMO service) to patients who received ECMO after the government-implemented national ECMO programme in April 2014.They reported that the use of ECMO was associated with lower in-hospital mortality (65% vs 100%; $P = 0.02$), better oxygenation [mean partial pressure of arterial oxygen/fraction of inspired oxygen ratio (Standard deviation [SD]) at days 7 and 14 of ICU admission: 124 (106.9) vs. 63 (66.1), and 237 (42.1) vs. 85 (31.9); $P < 0.05$] and less norepinephrine use (on days 1 and 14 of ICU admission: 29 vs. 80%, and 36 vs. 93%; $P < 0.05$) compared to historical controls who did not receive ECMO.[2] Whilst the use of ECMO appears to be safe in MERS-CoV patients with refractory hypoxemia and may confer overall benefit, reports on these are only limited to small case series and retrospective studies.

Patient Selection for ECMO—Ethical Considerations and Prediction Scoring Systems in a Pandemic

The considerations behind resource allocation in a mass-casualty environment are complex and challenging.[59–61] In 2006, modelling studies suggested that an event of similar scale to the 1918 Influenza pandemic would require 400% of existing ICU beds and 200% of mechanical ventilators in the United States.[62] Subsequent disasters such as Hurricane Katrina and the H1N1pdm09 pandemic also demonstrated the tremendous strain borne by healthcare systems.[59,63] In the wake of acts of terrorism, natural disasters and infectious outbreaks that have threatened to overwhelm healthcare infrastructure, what has become clear is the need for comprehensive pre-disaster planning and preparation at national and institutional levels, with the goals of developing: 1) guidance for the rights and responsibilities of healthcare workers; 2) healthcare infrastructure, supplies, training and protocols for surge capacity; 3) inter-agency collaboration, communication and workflows; 4) simulation exercises to further test and enhance systems; 5) accepted altered standards of care in resource-deficient circumstances; 6) public acceptance of revised workflows and; 7) post-disaster evaluation, accountability and staff care plans.[59,62,64–6]

As a limited, resource-intensive, potentially life-saving treatment that is not universally available, patient selection for ECMO comes under even greater scrutiny. This challenge is compounded not only by improvements in ECMO and other rescue therapies in critical care, resulting in evolving indications for ECMO,[67] but also by the ongoing examination of the benefit of ECMO compared to conventional therapies in various clinical settings.[63] In addition to employing clinical judgement, there are 2 broad approaches to guide patient selection for ECMO in a pandemic with limited resources; 1) the use of ethical principles and; 2) the use of predictive scoring systems to risk-stratify patients.

Outside of a crisis, standard resource allocation strategies typically adopt the "first-come-first-serve" approach and focus on patients with the greatest potential for benefit. However, in a pandemic where resources and infrastructure cannot meet demand, a commonly adopted strategy is to achieve the "greatest good for the greatest number". While certainly an important overarching principle in resource-limited settings, adopting the "greatest good for the greatest number" as a sole allocation principle does not adequately encompass other ethically relevant considerations, which include: 1) broad social value; 2) instrumental value; 3) maximising life years and; 4) the life cycle principle (Table 4).[59,60]

As no single ethical principle can sufficiently address the diverse moral dilemmas likely to arise in a pandemic, it seems reasonable to adopt a multi-principle allocation system. We believe that this combination of ethical principles will encompass a holistic approach to patient selection for a limited, resource-intensive therapy such as ECMO in a pandemic. Whilst the ideal situation may call for advocacy of combining the principles of "greatest

Table 4. Ethical Principles to Guide Resource Allocation in a Pandemic

Principle	Allocation Strategy
Greatest good for the greatest number	• Shift focus of care from the patient to the community at large • May be interpreted in different ways: ▪ Maximise the number of lives saved ▪ Allocate care to achieve maximal benefit with minimal resources ▪ May result in denying resources to groups of people who are deemed "not worth" saving
Broad social value	• Refers to one's overall worth to society • Involves using summary judgements about an individuals' past to determine potential future contributions to society • Difficult to engage the public to agree upon a criterion to assign societal worth • Negates the egalitarian view that all individuals have a right to treatment
Instrumental value	• Refers to ability of individuals to perform specific functions that are essential in a time of crisis • Also known as the "multiplier effect" where prioritising the care of key individuals leads to preservation of more lives through their work • However, key individuals may not recover in a timely manner to fulfil their roles • Difficult to identify roles and key individuals perceived to have instrumental value in a pandemic
Maximise life years	• Refers to prioritising care for an individual with the greatest chance of surviving for the longest time, thus preserving the greatest number of years of life • Already incorporated into strategies for allocating organs for transplantation, where recipients are selected based both on medical need and their expected duration of survival
Life cycle principle	• Refers to giving each individual an equal opportunity to live through various phases of life • Also known as the "fair innings" argument and "intergenerational equity" • Prioritises the young over the elderly, sacrificing experience for youth • A familiar concept where people believe that the young should be prioritised over the elderly in the face of limited resources

good for the greatest number", "maximising life years" and "the life cycle principle", a more likely scenario is that we are forced to be in a situation where we need to modify our current guidelines, accept less than normal standard of care in some cases and accept a "first-come-first-served" approach.

Scoring systems have long been used in critical and emergency care and multiple attempts have been made to adapt scoring systems to triage patients for critical care, MV and ECMO. While several scoring systems for ECMO in severe ARF have certainly demonstrated promising results, all of them, by their nature, share similar limitations[68–80] (Tables 5 and 6 for Paediatric and Adult scores, respectively). Most scoring systems have been developed in small and restricted derivation cohorts and lack external validation, with variable performance in different cohorts of patients. Their validity may also be challenged over time with further improvements in diagnostic and therapeutic modalities. Ultimately, the intent of these scores are to quantify and analyse cohorts of patients, not to reliably predict outcomes when applied to individual patients.[81] Several studies evaluating the performance of predictive scores when retrospectively applied, have demonstrated that these scores overpredicted mortality.[81] In other words, patients who may have had a significant chance of survival would have been erroneously denied critical care. This does not mean that scoring systems have no place in deciding resource allocation, but that clinicians must remain aware that such scores are imperfect. At present, predictive scores for ECMO in ARDS will likely best serve as an initial screen and adjunct to experienced clinical assessment and decision making. Whether these scores ultimately enhance patient selection for ECMO in a pandemic remains to be determined.

Lessons Learnt to Apply for ECMO in COVID-19

ECMO and MV are not disease-modifying therapies in themselves, but rather, life-sustaining support systems that allow time for other interventions to correct the underlying pathology. In the absence of definitive treatment for ARDS secondary to COVID-19, we are compelled to focus on mitigating risk of further harm and optimising conditions, not just for survival, but for survival with good neurological and functional recovery. Initial steps in this endeavour would involve capitalising on the benefits of ECMO in ARDS to minimise VILI, titrate fluid status, optimise nutrition and initiate early neurorehabilitation in the ICU.[82,83] However, if the natural history of COVID-19 amongst critically ill patients tends to progress towards

Table 5. Summary of Paediatric Predictive Scoring Systems for Survival for ECMO in Acute Respiratory Failure

Score, Year	Cohort Characteristics/ ECMO Mode	PreECMO Variables	Internal Validation (AUROC)	External Validation (AUROC)
PIPER, 2016*	ELSO Registry 2000–10 (n = 1501): <30 days old with respiratory failure, mortality 37%, VA 100%	Age, APGAR at 5 minutes, birth weight, mean arterial blood pressure, PaO_2, pH, inhaled nitric oxide use	0.73 (0.70 – 0.75)	-
Neo-RESCUERS, 2016†	ELSO Registry 2008–13 (n = 3139): <28 days old with respiratory failure, mortality 31%, VA 65%, VV 35%	Age, birth weight, comorbidities, gender, gestational age, PaO_2/FiO_2 ratio, pH, primary diagnosis, renal failure, inhaled nitric oxide use	0.78 (0.76 – 0.79)	-
Ped-RESCUERS, 2016‡	ELSO Registry 2009–14 (n = 1611): 29 days to <18 years old with respiratory failure, mortality 39.8%‖	Diagnosis (of asthma, bronchiolitis, malignancy and pertussis), hours admitted, hours intubated, mean airway pressure, $PaCO_2$, pH, milrinone use, ventilator type	0.69 (0.67 – 0.71)	-
P-PREP, 2017§	ELSO Registry 2001–13 (n = 4352): >7 days to <18 years old with PARDS, mortality 43%, VA 57%, VV 43%	Comorbidities, duration of MV, mode of ECMO, primary pulmonary diagnosis, PaO_2/FiO_2 ratio, pH	0.69 (0.67 – 0.71)	0.69 (0.67 – 0.71)¶

APGAR: Appearance, pulse, grimace, activity and respiration; AUROC: Area under receiver operating characteristic curve; ELSO: Extracorporeal Life Support Organization; ECMO: Extracorporeal membrane oxygenation; FiO_2: Fraction of inspired oxygen; MV: Mechanical ventilation; $PaCO_2$: Partial pressure of arterial carbon dioxide; PaO_2: Partial pressure of arterial oxygen; PARDS: Paediatric acute respiratory distress syndrome; VA: Veno-arterial; VV: Veno-venous

*Maul TM, Kuch BA, Wearden PD. Development of risk indices for neonatal respiratory extracorporeal membrane oxygenation. ASAIO J 2016;62: 584–90.

†Barbaro RP, Bartlett RH, Chapman RL, Paden ML, Roberts LA, Gebremariam A, et al. Development and validation of the Neonatal Risk Estimate Score for Children Using Extracorporeal Respiratory Support. J Pediatr 2016;173:56–61.

‡Barbaro RP, Boonstra PS, Paden ML, Roberts LA, Annich GM, Bartlett RH, et al. Development and validation of the Pediatric Risk Estimate Score for Children Using Extracorporeal Respiratory Support (Ped-RESCUERS). Intensive Care Med 2016;42:879–88.

§Bailly DK, Reeder RW, Zabrocki LA, Hubbard AM, Wilkes J, Bratton SL, et al. Development and validation of a score to predict mortality in children undergoing extracorporeal membrane oxygenation for respiratory failure: Pediatric Pulmonary Rescue with Extracorporeal Membrane Oxygenation Prediction score. Crit Care Med 2017;45:e58–66.

‖Mode of ECMO used was not specified

¶Validation with an independent cohort of 2007 patients by Bailly et al.[71]

distributive shock with refractory multi-organ failure, the role of ECMO may be limited.[84]

At present, there are limited detailed reports on the use of ECMO in COVID-19.[3,4,85] Based on recent clinical data related to COVID-19, previous studies and recommendations from ELSO, the Chinese Society of Extracorporeal Life Support (CSECLS) has recently drafted a series of recommendations for the use of ECLS for critically ill patients with COVID-19[86] (Table 7). While providing clear and objective indications for ECLS, these recommendations lack guidance for optimal MV strategy. Considering that the majority of deaths from ARDS are caused by sepsis and multi-organ failure (MOF)[87] and that there is emerging evidence of VILI contributing to MOF,[88] we should focus on identifying and adhering to the optimal mode of LPV while on ECMO support. Whether this ideal LPV strategy to minimise VILI turns out to be ultra-low TV of <3 mL/kg, apnoeic oxygenation with PEEP or even individualised electrical impedance tomography-guided MV, it is biologically plausible and reasonable to take advantage of the support provided by ECMO to further reduce MV settings from the current accepted standard of LPV.[82] We eagerly await the results of ongoing trials assessing the role of ultra-low TV in ARDS to provide further guidance.[18,19] The need to rely on evidence derived outside of a respiratory pandemic must be recognised, given the numerous challenges of conducting large, multi-centre trials in resource-limited settings. While this might limit the applicability of study findings, we may have no other choice but to extrapolate such findings to patients in future pandemics. Efforts to minimise VILI and consequent MOF should also be coupled with strict adherence to infection control precautions to reduce the incidence of intercurrent sepsis, ventilator-associated pneumonia and nosocomial transmission of COVID-19 to healthcare workers. This is especially important, given that up to 40% of a reported COVID-19 cohort were attributed to nosocomial transmission.[3]

Table 6. Summary of Adult Predictive Scoring Systems for Survival for ECMO in Acute Respiratory Failure

Score, Year	Cohort Characteristics/ ECMO Mode	PreECMO Variables	Internal Validation (AUROC)	External Validation (AUROC)
ECMOnet, 2013*	Italian cohort 2009 (n = 60): H1N1 ARDS, mortality 32%, VA 2%, VV 98%,	Bilirubin, haematocrit, hospital LOS, mean arterial blood pressure, serum creatinine	0.86 (0.75 – 0.96)	0.69 (0.56 – 0.83)** 0.60 (0.54 – 0.67)†† 0.51 (0.37 – 0.66)‡‡ 0.69 (0.59 – 0.79)§§
Roch, 2013†	French cohort 2009–13 (n = 85): ARDS, mortality 56%, VA 9%, VV 91%	Age, diagnosis of influenza, pneumonia, SOFA score	0.80 (0.71 – 0.89)	0.70 (0.56 – 0.83)‡‡ 0.55 (0.45 – 0.70)‖‖ 0.56 (0.45 – 0.68)§§
PRESERVE, 2013‡	French cohort 2008–12 (n = 140): ARDS, mortality at 6 months 40%, VA 5%, VV 95%	Age, body mass index, immunocompromised status, MV duration, PEEP, plateau pressure, SOFA score, use of prone positioning	0.89 (0.83 – 0.94) [to predict 6-month survival]	0.68 (0.62 – 0.75)†† 0.80 (0.66 – 0.90)‡‡ 0.64 (0.51 – 0.77)‖‖ 0.59 (0.48 – 0.71)§§
Enger, 2014§	German cohort 2008–13 (n = 304): acute respiratory failure, mortality 38%, VV 100%	Age, haemoglobin, immunocompromised status, lactate, minute ventilation on MV	0.75 (0.69 – 0.80)	–
RESP, 2014‖	ELSO Registry 2000–12 (n = 2355): acute respiratory failure, mortality 43%, VA or mixed modes 18%, VV 82%	Acute non-pulmonary infection, acute respiratory diagnosis, age, cardiac arrest, CNS dysfunction, immunocompromised status, inhaled nitric oxide use, MV duration, $PaCO_2$, PIP, use of bicarbonate infusion, use of paralysis	0.74 (0.72 – 0.76)	0.92 (0.89 – 0.97)¶¶ 0.79 (0.65 – 0.89)‡‡ 0.69 (0.60 – 0.79)## 0.69 (0.58 – 0.81)‖‖ 0.64 (0.53 – 0.75)§§
VV-ECMO mortality score, 2016¶	Taiwanese cohort 2007–15 (n = 116): acute respiratory failure, mortality 47%, VV 100%	Immunocompromised status, MV duration, SOFA score	0.76 (0.67 – 0.85)	–
PRESET, 2017#	German cohort 2010–15 (n = 108): ARDS, mortality 62%, VV 100%	Hospital LOS, lactate, mean arterial blood pressure, pH, platelet count	0.85 (0.76 – 0.93)	0.70 (0.56 – 0.83)***

ARDS: Acute respiratory distress syndrome; AUROC: Area under receiver operating characteristic curve; CNS: Central nervous system; ELSO: Extracorporeal Life Support Organization; ECMO: Extracorporeal membrane oxygenation; FiO_2: Fraction of inspired oxygen; LOS: Length of stay; MV: Mechanical ventilation; $PaCO_2$: Partial pressure of arterial carbon dioxide; PaO_2: Partial pressure of arterial oxygen; PEEP: Positive end-expiratory pressure; PIP: Peak inspiratory pressure; SOFA: Sequential organ failure assessment; VA: Veno-arterial; VV: Veno-venous

*Pappalardo F, Pieri M, Greco T, Patroniti N, Pesenti A, Arcadipane A, et al. Predicting mortality risk in patients undergoing venovenous ECMO for ARDS due to influenza A (H1N1) pneumonia: the ECMOnet score. Intensive Care Med 2013;39:275–81.

†Roch A, Hraiech S, Masson E, Grisoli D, Forel JM, Boucekine M, et la. Outcome of acute respiratory distress syndrome patients treated with extracorporeal membrane oxygenation and brought to a referral center. Intensive Care Med 2014;40:74–83.

‡Schmidt M, Zogheib E, Roze H, Repesse X, Lebreton G, Luyt CE, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Intensive Care Med 2013;39:1704–13.

§Enger T, Philipp A, Videm V, Lubnow M, Wahba A, Fischer M, et al. Prediction of mortality in adult patients with severe acute lung failure receiving veno-venous extracorporeal membrane oxygenation: a prospective observational study. Crit Care 2014;18:R67.

‖Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. Am J Respir Crit Care Med 2014;189:1374–82.

¶Cheng YT, Wu MY, Chang YS, Huang CC, Lin PJ. Developing a simple preinterventional score to predict hospital mortality in adult venovenous extracorporeal membrane oxygenation: a pilot study. Medicine (Baltimore). 2016;95:e4380.

#Hilder M, Herbstreit F, Adamzik M, Beiderlinden M, Burschen M, Peters J, et al. Comparison of mortality prediction models in acute respiratory distress syndrome undergoing extracorporeal membrane oxygenation and development of a novel prediction score: the PREdiction of Survival on ECMO Therapy-Score (PRESET-Score). Crit Care 2017;21:301.

**Validation in an independent cohort of 74 patients by Papparlardo et al.[72]

††Validation in a cohort by Enger et al.[75]

‡‡Validation in a cohort of 50 patients by Lee et al.[79]

§§Validation in a cohort of 108 patients by Hilder et al.[78]

‖‖Validation in a cohort of 99 patients by Kang et al.[80]

¶¶Validation in an independent cohort of 140 patients by Schmidt et al.[76]

##Validation in a cohort of 116 patients by Cheng et al.[77]

***Validation in an independent cohort of 59 patients by Hilder et al.[78]

Table 7. Summary of Recommendations for Extracorporeal Life Support for COVID-19 from the Chinese Society of Extracorporeal Life Support*

Recommendation	Description
Indications for ECMO	• Hypoxemia despite maximal conventional mechanical ventilation (FiO_2 ≥0.8, TV 6 mL/kg, PEEP ≥10 cmH_2O) with at least 1 of the following conditions met: ▪ PaO_2/FiO_2 ratio <50 for >3 hours ▪ PaO_2/FiO_2 ratio <80 for >6 hours ▪ PaO_2/FiO_2 ratio <100 when FiO_2 = 1.0 ▪ Arterial pH <7.25, $PaCO_2$ >60 mmHg for >6 hours and RR >35 breaths/min ▪ Arterial pH <7.2 with Pplat >30 cmH_2O and RR >35 breaths/min ▪ Air leak syndrome • Cardiogenic shock or cardiac arrest
Relative contraindications	• Combination of irreversible disease, severe central nervous system damage or advanced-stage malignancy • Coagulopathy • Mechanical ventilation at high settings (FiO2 >0.9, Pplat >30 cmH2O) lasting ≥7 days • Severe multiple organ failure • Moderate to severe aortic regurgitation and acute aortic dissection could be considered contraindications to VA-ECMO support • Pharmacologic immunosuppression (absolute neutrophil count <0.4 × 109/L) • Lack of vascular access to ECMO cannulation due to altered anatomy or vascular pathology • While advanced age was not considered an actual contraindication, it is associated with increased mortality risk
Circuit configuration	• VV-ECMO is preferred in normal cardiac function • VA-ECMO may be considered if cardiogenic shock or cardiac arrest occurs • VAV-ECMO may be considered in differential hypoxia between upper and lower body

COVID-19: Coronavirus disease 2019; ECMO: Extracorporeal membrane oxygenation; FiO_2: Fraction of inspired oxygen; $PaCO_2$: Partial pressure of arterial carbon dioxide; PaO_2: Partial pressure of arterial oxygen; PEEP: Positive end-expiratory pressure; Pplat: Plateau pressure; RR: Respiratory rate; TV: Tidal volume; VA: Veno-arterial; VAV: Veno-arterial-venous; VV: Veno-venous

*Chinese Society of Extracorporeal Life Support. Recommendations on extracorporeal life support for critically ill patients with novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi 2020;43:E009.

The expansion in ECMO use during the H1N1pdm09 pandemic has highlighted the importance of collaboration within and between institutions to establish and strengthen ECMO capabilities to optimise outcomes. Key steps to institute in the COVID-19 epidemic include the preparation of designated high-volume expert ECMO centres, establishment of ECMO transport services with clear criteria for timely referral and transfer of critically ill patients, as well as simulation training to test and enhance knowledge, skill and workflows. However, ECMO transport services should be centrally coordinated, with a dynamic criterion for ECMO based on resource availability, so as to prevent ECMO centres from being overwhelmed.[84] The expanding use of ECMO must also be accompanied by efforts to reduce its associated risks. For example, the use of biocompatible circuits and hollow-fibre oxygenators have contributed to a reduced need for anticoagulation.[7] This is demonstrated by the recent EOLIA trial, where severe bleeding complications were rare, with a 2% incidence of haemorrhagic stroke in the ECMO group, compared to 4% in the non-ECMO group.[14] Finally, national and institutional protocols must be provided to guide physician decisions regarding resource-allocation and patient selection for ECMO for critically ill patients with COVID-19, ideally by considering multiple ethical principles in conjunction with the use of prediction scoring systems and expert clinical judgement.

Conclusion

The role of ECMO for ARDS secondary to respiratory epidemics and pandemics has expanded and continues to grow. While the majority of patients with COVID-19 have had mild disease, a significant proportion become critically ill and develop ARDS and circulatory compromise. Despite equipoise regarding the benefit of ECMO in ARDS and the lack of robust evidence for optimal MV techniques and infection control, recent and emerging research continue to be encouraging, highlighting the importance of capitalising on ECMO support to minimise VILI and MOF, as well as improvements in technology and practices to reduce the risks of ECMO. We may need to rely on evidence for ECMO derived outside of a respiratory pandemic, given the challenges of conducting large, multi-centre trials in resource-limited settings. Moral dilemmas regarding patient selection for ECMO in a resource-deficient setting may undermine various aspects of the healthcare system. Thus, it is critical to prepare and develop protocols and surge capacity for future pandemics, as well as craft

guidelines for patient selection, using multiple ethical principles and prediction scores to complement expert clinical judgement.

REFERENCES

1. Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, et al. Critically ill patients with 2009 influenza A (H1N1) infection in Canada. JAMA 2009;302:1872–9.
2. Alshahrani MS, Sindi A, Alshamsi F, Al-Omari A, El Tahan M, Alahmadi B, et al. Extracorporeal membrane oxygenation for severe Middle East respiratory syndrome coronavirus. Ann Intensive Care 2018;8:3.
3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;doi:10.1001/jama.2020.1585.
4. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centre, retrospective, observational study. Lancet Respir Med 2020;doi:10.1016/S2213-2600(20)30079-5.
5. Goh KJ, Choong MCM, Cheong EHT, Kalimuddin S, Duu Wen S, Phua GC, et al. Rapid progression to acute respiratory distress syndrome: review of current understanding of critical illness from COVID-19 infection. Ann Acad Med Singapore 2020;49:108–18.
6. Brodie D, Slutsky AS, Combes A. Extracorporeal life support for adults with respiratory failure and related indications: a review. JAMA 2019;322:557–68.
7. Cavayas YA, Thakore A, Fan E. Extracorporeal strategies in acute respiratory distress syndrome. Semin Respir Crit Care Med 2019; 40:114–28.
8. Gattinoni L, Quintel M, Marini JJ. Volutrauma and atelectrauma: which is worse? Crit Care 2018;22:264.
9. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301–8.
10. Jouvet P, Thomas NJ, Wilson DF, Erickson S, Khemani R, Zimmerman J, et al. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med 2015;16:428–39.
11. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107–16.
12. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;195:1253–63.
13. Protti A, Andreis DT, Monti M, Santini A, Sparacino CC, Langer T, et al. Lung stress and strain during mechanical ventilation: any difference between statics and dynamics? Crit Care Med 2013;41:1046–55.
14. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378:1965–75.
15. Schmidt M, Stewart C, Bailey M, Nieszkowska A, Kelly J, Murphy L, et al. Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome: a retrospective international multicenter study. Crit Care Med 2015;43:654–64.
16. Needham DM, Colantuoni E, Mendez-Tellez PA, Dinglas VD, Sevransky JE, Himmelfarb CRD, et al. Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. BMJ 2012;344:e2124.
17. Araos J, Alegria L, Garcia P, Cruces P, Soto D, Erranz B, et al. Near-apneic ventilation decreases lung injury and fibroproliferation in an acute respiratory distress syndrome model with extracorporeal membrane oxygenation. Am J Respir Crit Care Med 2019;199:603–12.
18. Combes A, Ranieri M. Strategy of ultraprotective lung ventilation with extracorporeal CO_2 Removal for New-Onset Moderate to Severe ARDS (SUPERNOVA). Available at: https://clinicaltrials.gov/ct2/show/NCT02282657. Accessed on 13 February 2020.
19. Mcauley D, McNamee JJ. Protective ventilation with veno-venous lung assist in respiratory failure (REST). Available at: https://clinicaltrials.gov/ct2/show/NCT02654327. Accessed on 13 February 2020.
20. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372:747–55.
21. Pham T, Combes A, Rozé H, Chevret S, Mercat A, Roch A, et al. Extracorporeal membrane oxygenation for pandemic influenza A (H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. Am J Respir Crit Care Med 2013;187:276–85.
22. Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, et al. High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 2013;368:795–805.
23. Young D, Lamb SE, Shah S, MacKenzie I, Tunnicliffe W, Lall R, et al. High-frequency oscillation for acute respiratory distress syndrome. N Engl J Med 2013;368:806–13.
24. El-Nawawy A, Moustafa A, Heshmat H, Abouahmed A. High frequency oscillatory ventilation versus conventional mechanical ventilation in pediatric acute respiratory distress syndrome: a randomized controlled study. Turk J Pediatr 2017;59:130–43.
25. Wong JJ, Liu S, Dang H, Anantasit N, Phan PH, Phumeetham S, et al. The impact of high frequency oscillatory ventilation on mortality in paediatric acute respiratory distress syndrome. Crit Care 2020;24:31.
26. Wong JJ, Phan HP, Phumeetham S, Ong JSM, Chor YK, Qian S, et al. Risk stratification in pediatric acute respiratory distress syndrome: a multicenter observational study. Crit Care Med 2017;45:1820–28.
27. Khemani RG, Conti D, Alonzo TA, Bart RD III, Newth CJ. Effect of tidal volume in children with acute hypoxemic respiratory failure. Intensive Care Med 2009;35:1428–37.
28. de Jager P, Burgerhof JG, van Heerde M, Albers MJ, Markhorst DG, Kneyber MC. Tidal volume and mortality in mechanically ventilated children: a systematic review and meta-analysis of observational studies. Crit Care Med 2014;42:2461–72.
29. Erickson S, Schibler A, Numa A, Nuthall G, Yung M, Pascoe E, et al. Acute lung injury in pediatric intensive care in Australia and New Zealand: a prospective, multicenter, observational study. Pediatr Crit Care Med 2007;8:317–23.
30. Biffi S, Di Bella S, Scaravilli V, Peri AM, Grasselli G, Alagna L, et al. Infections during extracorporeal membrane oxygenation: epidemiology, risk factors, pathogenesis and prevention. Int J Antimicrob Agents 2017;50:9–16.
31. Cavayas YA, Yusuff H, Porter R. Fungal infections in adult patients on extracorporeal life support. Crit Care 2018;22:98.
32. Extracorporeal Life Support Organization. Infectious Disease Task Force: Infection Control and Extracorporeal Life Support. Available at: https://www.elso.org/Portals/0/Files/Infection-Control-and-Extracorporeal-Life-Support.pdf. Accessed on 13 February 2020.
33. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis 2011;52:e162–93.

34. Seto WH, Tsang D, Yung RW, Ching TY, Ng TK, Ho M, et al. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). Lancet 2003;361:1519–20.
35. Tambyah PA, Tay J. The Middle East respiratory syndrome coronarvirus (MERS-CoV) and Singapore. Ann Acad Med Singapore 2013;42:376–8.
36. Leung TF, Ng PC, Cheng FW, Lyon DJ, So KW, Hon EK, et al. Infection control for SARS in a tertiary paediatric centre in Hong Kong. J Hosp Infect 2004;56:215–22.
37. Cheng VC, Chan JF, To KK, Yuen KY. Clinical management and infection control of SARS: lessons learned. Antiviral Res 2013;100:407–19.
38. Levy MM, Baylor MS, Bernard GR, Fowler R, Franks TJ, Hayden FG, et al. Clinical issues and research in respiratory failure from severe acute respiratory syndrome. Am J Respir Crit Care Med 2005;171:518–26.
39. Wilkes AR. Heat and moisture exchangers and breathing system filters: their use in anaesthesia and intensive care. Part 2—practical use, including problems, and their use with paediatric patients. Anaesthesia 2011;66:40–51.
40. Zhang H, Wang DX. Noninvasive measurement of carbon dioxide during one-lung ventilation with low tidal volume for two hours: end-tidal versus transcutaneous techniques. PLoS One 2015;10:e0138912.
41. Le DH, Bloom SA, Nguyen QH, Maloney SA, Le QM, Leitmeyer KC, et al. Lack of SARS transmission among public hospital workers, Vietnam. Emerg Infect Dis 2004;10:265–8.
42. Jiang S, Huang L, Chen X, Wang J, Wu W, Yin S, et al. Ventilation of wards and nosocomial outbreak of severe acute respiratory syndrome among healthcare workers. Chin Med J (Engl) 2003;116:1293–7.
43. Chan JF, To KK, Tse H, Jin DY, Yuen KY. Interspecies transmission and emergence of novel viruses: lessons from bats and birds. Trends Microbiol 2013;21:544–55.
44. Lew TW, Kwek TK, Tai D, Earnest A, Loo S, Singh K, et al. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. JAMA 2003;290:374–80.
45. Dominguez-Cherit G, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A, et al. Critically ill patients with 2009 influenza A(H1N1) in Mexico. JAMA 2009;302:1880–7.
46. Nehra D, Goldstein AM, Doody DP, Ryan DP, Chang Y, Masiakos PT. Extracorporeal membrane oxygenation for nonneonatal acute respiratory failure: the Massachusetts General Hospital experience from 1990 to 2008. Arch Surg 2009;144: 427–32.
47. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009;374:1351–63.
48. Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. JAMA 2009;302:1888–95.
49. Estenssoro E, Ríos FG, Apezteguía C, Reina R, Neira J, Ceraso DH, et al. Pandemic 2009 influenza A in Argentina: a study of 337 patients on mechanical ventilation. Am J Respir Crit Care Med 2010;182:41–8.
50. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA* 2011;306:1659–68.
51. Patroniti N, Zangrillo A, Pappalardo F, Peris A, Cianchi G, Braschi A, et al. The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: preparation for severe respiratory emergency outbreaks. Intensive Care Med 2011;37:1447–57.
52. Michaels AJ, Hill JG, Bliss D, Sperley BP, Young BP, Quint P, et al. Pandemic flu and the sudden demand for ECMO resources: a mature trauma program can provide surge capacity in acute critical care crises. J Trauma Acute Care Surg 2013;74:1493–7.
53. Turner DA, Williford WL, Peters MA, Thalman JJ, Shearer IR, Walczak RJ, et al. Development of a collaborative program to provide extracorporeal membrane oxygenation for adults with refractory hypoxemia within the framework of a pandemic. Pediatr Crit Care Med 2011;12:426–30.
54. Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen KY. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. Clin Microbiol Rev 2015;28:465–522.
55. World Health Organization. MERS-CoV Global Summary and Risk Assessment. Available at: https://www.who.int/emergencies/mers-cov/mers-summary-2016.pdf?ua=1. Accessed on 15 February 2020.
56. WHO MERS-CoV Research Group. State of knowledge and data gaps of Middle East respiratory syndrome coronavirus (MERS-CoV) in humans. PLoS Curr 2013;5:doi: 10.1371/currents.outbreaks.0bf719e352e7478f8ad85fa30127ddb8chan.
57. Al-Abdallat MM, Payne DC, Alqasrawi S, Rha B, Tohme RA, Abedi GR, et al. Hospital-associated outbreak of Middle East respiratory syndrome coronavirus: a serologic, epidemiologic, and clinical description. Clin Infect Dis 2014;59:1225–33.
58. Guery B, Poissy J, el Mansouf L, Sejourne C, Ettahar N, Lemaire X, et al. Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission. Lancet 2013;381:2265–72.
59. Holt GR. Making difficult ethical decisions in patient care during natural disasters and other mass casualty events. Otolaryngol Head Neck Surg 2008;139:181–6.
60. White DB, Katz MH, Luce JM, Lo B. Who should receive life support during a public health emergency? Using ethical principles to improve allocation decisions. Ann Intern Med 2009;150:132–8.
61. Tiong WW, Koh GC. Ethical considerations in the review of Singapore's H1N1 pandemic response framework in 2009. Ann Acad Med Singapore 2013;42:246–50.
62. Toner E, Waldhorn R, Maldin B, Borio L, Nuzzo JB, Lam C, et al. Hospital preparedness for pandemic influenza. Biosecur Bioterror 2006;4:207–17.
63. Dalton HJ, MacLaren G. Extracorporeal membrane oxygenation in pandemic flu: insufficient evidence or worth the effort? Crit Care Med 2010;38:1484–5.
64. Lum LH, Badaruddin H, Salmon S, Cutter J, Lim AY, Fisher D. Pandemic preparedness: nationally-led simulation to test hospital systems. Ann Acad Med Singapore 2016;45:332–7.
65. Hsu LY, Chia PY, Lim JFY. The novel coronavirus (SARS-CoV-2) epidemic. Ann Acad Med Singapore 2020;49:105–7.
66. Ho CSH, Chee CY, Ho RCM. Mental health strategies to combat the psychological impact of COVID-19 beyond paranoia and panic. Ann Acad Med Singapore 2020;49:155–60.
67. Custer JR. The evolution of patient selection criteria and indications for extracorporeal life support in paediatric cardiopulmonary failure: next time, let's not eat the bones. Organogenesis 2011;7:13–22.
68. Maul TM, Kuch BA, Wearden PD. Development of risk indices for neonatal respiratory extracorporeal membrane oxygenation. ASAIO J 2016;62:584–90.
69. Barbaro RP, Bartlett RH, Chapman RL, Paden ML, Roberts LA, Gebremariam A, et al. Development and validation of the Neonatal Risk Estimate Score for Children Using Extracorporeal Respiratory Support. J Pediatr 2016;173:56–61.

70. Barbaro RP, Boonstra PS, Paden ML, Roberts LA, Annich GM, Bartlett RH, et al. Development and validation of the Pediatric Risk Estimate Score for Children Using Extracorporeal Respiratory Support (Ped-RESCUERS). Intensive Care Med 2016;42:879–88.

71. Bailly DK, Reeder RW, Zabrocki LA, Hubbard AM, Wilkes J, Bratton SL, et al. Development and validation of a score to predict mortality in children undergoing extracorporeal membrane oxygenation for respiratory failure: Pediatric Pulmonary Rescue with Extracorporeal Membrane Oxygenation Prediction score. Crit Care Med 2017;45:e58–66.

72. Pappalardo F, Pieri M, Greco T, Patroniti N, Pesenti A, Arcadipane A, et al. Predicting mortality risk in patients undergoing venovenous ECMO for ARDS due to influenza A (H1N1) pneumonia: the ECMOnet score. Intensive Care Med 2013;39:275–81.

73. Roch A, Hraiech S, Masson E, Grisoli D, Forel JM, Boucekine M, et la. Outcome of acute respiratory distress syndrome patients treated with extracorporeal membrane oxygenation and brought to a referral center. Intensive Care Med 2014;40:74–83.

74. Schmidt M, Zogheib E, Roze H, Repesse X, Lebreton G, Luyt CE, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Intensive Care Med 2013; 39:1704–13.

75. Enger T, Philipp A, Videm V, Lubnow M, Wahba A, Fischer M, et al. Prediction of mortality in adult patients with severe acute lung failure receiving veno-venous extracorporeal membrane oxygenation: a prospective observational study. Crit Care 2014;18:R67.

76. Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. Am J Respir Crit Care Med 2014;189:1374–82.

77. Cheng YT, Wu MY, Chang YS, Huang CC, Lin PJ. Developing a simple preinterventional score to predict hospital mortality in adult venovenous extracorporeal membrane oxygenation: a pilot study. Medicine (Baltimore). 2016;95:e4380.

78. Hilder M, Herbstreit F, Adamzik M, Beiderlinden M, Burschen M, Peters J, et al. Comparison of mortality prediction models in acute respiratory distress syndrome undergoing extracorporeal membrane oxygenation and development of a novel prediction score: the PREdiction of Survival on ECMO Therapy-Score (PRESET-Score). Crit Care 2017;21:301.

79. Lee S, Yeo HJ, Yoon SH, Lee SE, Cho WH, Jeon DS, et al. Validity of outcome prediction scoring systems in Korean patients with severe adult respiratory distress syndrome receiving extracorporeal membrane oxygenation therapy. J Korean Med Sci 2016;31:932–8.

80. Kang HR, Kim DJ, Lee J, Cho YJ, Kim JS, Lee SM, et al. A comparative analysis of survival prediction using PRESERVE and RESP Scores. Ann Thorac Surg 2017;104:797–803.

81. Adeniji KA, Cusack R. The Simple Triage Scoring System (STSS) successfully predicts mortality and critical care resource utilization in H1N1 pandemic flu: a retrospective analysis. Crit Care 2011;15:R39.

82. Gattinoni L, Tonetti T, Quintel M. How best to set the ventilator on extracorporeal membrane lung oxygenation. Curr Opin Crit Care 2017;23:66–72.

83. Abrams D, Schmidt M, Pham T, Beitler JR, Fan E, Golgher EC, et al. Mechanical ventilation for ARDS during extracorporeal life support: research and practice. Am J Respir Crit Care Med 2020;201:514–25.

84. MacLaren G, Fisher D, Brodie D. Preparing for the most critically ill patients with COVID-19. The potential role of extracorporeal membrane oxygenation. JAMA 2020;doi:10.1001/jama.2020.2342.

85. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.

86. Chinese Society of Extracorporeal Life Support. Recommendations on extracorporeal life support for critically ill patients with novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi 2020;43:E009.

87. Stapleton RD, Wang BM, Hudson LD, Rubenfeld GD, Caldwell ES, Steinberg KP. Causes and timing of death in patients with ARDS. Chest 2005;128:525–32.

88. Quilez ME, Lopez-Aguilar J, Blanch L. Organ crosstalk during acute lung injury, acute respiratory distress syndrome, and mechanical ventilation. Curr Opin Crit Care 2012;18:23–8.

89. Guerin C, Reignier J, Richard J-C, Beuret P, Gacouin A, Boulain T, et al. PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159–68.

90. Cavalcanti AB, Suzumura EA, Laranjeira LN, Paisani DM, Damiani LP, Guimaraes HP, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2017;318:1335–45.

91. Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Available at: https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US. Accessed on 27 March 2020.

Review Article

Sedation and Delirium in the Intensive Care Unit—A Practice-Based Approach

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Abstract

Introduction: Critically ill patients often require sedation for comfort and to facilitate therapeutic interventions. Sedation practice guidelines provide an evidence-based framework with recommendations that can help improve key sedation-related outcomes. Materials and Methods: We conducted a narrative review of current guidelines and recent trials on sedation. Results: From a practice perspective, current guidelines share many limitations including lack of consensus on the definition of light sedation, optimal frequency of sedation assessment, optimal timing for light sedation and consideration of combinations of sedatives. We proposed several strategies to address these limitations and improve outcomes: 1) early light sedation within the first 48 hours with time-weighted monitoring (overall time spent in light sedation in the first 48 hours—sedation intensity—has a dose-dependent relationship with mortality risk, delirium and time to extubation); 2) provision of analgesia with minimal or no sedation where possible; 3) a goal-directed and balanced multimodal approach that combines the benefits of different agents and minimise their side effects; 4) use of dexmedetomidine and atypical antipsychotics as a sedative-sparing strategy to reduce weaning-related agitation, shorten ventilation time and accelerate physical and cognitive rehabilitation; and 5) a bundled approach to sedation that provides a framework to improve relevant clinical outcomes. Conclusion: More effort is required to develop a practical, time-weighted sedation scoring system. Emphasis on a balanced, multimodal appraoch that targets light sedation from the early phase of acute critical illness is important to achieve optimal sedation, lower mortality, shorten time on ventilator and reduce delirium.

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Key words: Analgesia, Benzodiazepine, Critical Care, Dexmedetomidine, Propofol

Introduction

Sedation is the depression of patients' awareness of their environment and reduction of their responsiveness to external stimuli.[1] The use of analgesia and sedation in the intensive care unit (ICU) enables patients to tolerate painful and distressing procedures such as endotracheal intubation, invasive mechanical ventilation and insertion of invasive lines.[2] Deep sedation is sometimes necessary to manage significant agitation and distress, ventilator synchronisation, convulsive disorders, high intracranial pressure, shivering during therapeutic hypothermia and to provide amnesia during neuromuscular blockade.

There is growing evidence that sedation practices impact delirium which may increase ICU mortality and adversely affect long-term outcomes in ICU survivors.[3–6] With advancement in ventilator triggering and modes, the need for deep sedation in the critically ill has declined. There is a growing emphasis on lighter levels of sedation and early physical activity in the respective guidelines. In this report, we provide a narrative review

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and update on strategies to achieve optimal sedation and reduce the burden of coma and delirium in critically ill patients. We conclude with a brief consideration of sedation practice in Singapore.

Current Guidelines

The 2018 practice guidelines for the prevention and management of Pain, Agitation/sedation, Delirium, Immobility and Sleep disruption (PADIS)[7] recommend a protocol-based, stepwise assessment of pain and sedation management in critically ill adults with an analgesia-first principle (Table 1). Provision of light sedation facilitates spontaneous breathing, shortens ventilation time and early mobilisation.

Propofol or dexmedetomidine is preferred in mechanically ventilated patients while benzodiazepines should be avoided. Dexmedetomidine offers shorter median duration of mechanical ventilation,[8] shorter time to extubation and less delirium[9] than benzodiazepine. However, there was no difference in median duration of mechanical ventilation between propofol and dexmedetomidine.[8] The role of benzodiazepine in specific subgroups of patients—such as alcohol withdrawal—requires further study.

Although the PADIS guidelines present contemporary evidence-based recommendations and suggestions to improve sedation-related outcomes, they are not without limitations from a practice perspective which merit consideration.

First: Lack of Consensus Definition of Light Sedation

Ideally, light sedation should induce wakeful, comfortable and calm patients who are able to sustain attention and follow commands. Patients should be oriented to their surroundings and are able to communicate and cooperate with caregivers in early rehabilitation, mobilisation and return to normal cognitive and physical functions.

Various sedation scales are used in different health settings. The Richmond Agitation and Sedation Scale (RASS) and Riker Sedation-Agitation Scale (SAS) have been well validated in ventilated patients. Although a universally accepted range for light sedation is lacking, a RASS score of between +1 (slightly restless) to −2 (awake with eye contact to voice)—which corresponds to a SAS score of between 4 (calm and cooperative) to 3 (difficult to rouse and obeys simple commands)—is generally considered as being within the acceptable range.

Table 1. Summary of Recommendations on Pain and Agitation/Sedation by PADIS

Recommendation	Strength of Recommendation	Quality of Evidence
Pain		
Pain in adult ICU patients should be treated before a sedative agent is considered and the management of pain should be guided by routine pain assessment (analgesia-first sedation or analgesia-based sedation)	NA (Good practice statement)	NA
Use a stepwise approach for pain and sedation management that is protocol-based and assessment-driven	Conditional	Moderate
Agitation/sedation		
Use light sedation (vs deep sedation) in mechanically ventilated adults	Conditional	Low
Use propofol over benzodiazepine in adult ICU patients who are mechanically ventilated after cardiac surgery	Conditional	Low
Use either propofol or dexmedetomidine over benzodiazepines in mechanically ventilated adults	Conditional	Low
In intubated adults, daily sedation interruptions and nurse-led targeted sedation can achieve and maintain a light level of sedation	Ungraded	Ungraded
BIS monitoring appears best suited for sedative titration during deep sedation or neuromuscular blockade, although observational data also suggest lighter sedation has potential benefit	Ungraded	Ungraded
Sedation monitored with BIS compared with subjective scales may improve sedative titration when a sedative scale cannot be used	Ungraded	Ungraded
Physical restraints are frequently used to prevent self-extubation and medical device removal, avoid falls and protect staff from combative patients despite a lack of studies that demonstrated the efficacy and safety concerns associated with physical restraints	Ungraded	Ungraded

BIS: Bispectral Index; ICU: Intensive Care Unit; NA: Not applicable; PADIS: Pain, Agitation/sedation, Delirium, Immobility and Sleep disruption

Despite being widely accepted as the gold standard in current sedation monitoring, the subjective nature of RASS and SAS assessments predisposed both scales to variability and uncertainty on the exact level of sedation that is needed at any point in time; with lower RASS scores, variable inter-rater reliability becomes particularly glaring in different institutions.[10–12]

Second: Optimal Frequency of Sedation Assessment is Not Known

There is a lack of consensus on the frequency of sedation assessments. The intermittent nature of these assessments makes it problematic to observe any rapid change in sedation status in response to sedative bolus.

The sedation score indicates the condition of the patient when it was taken, and often does not reflect the level of sedation the patient would be at throughout the day. This is because the clinical status of the patient fluctuates with the course of disease and ICU stay.

Third: Optimal Timing of Light Sedation is Not Defined

Although the PADIS guidelines suggest that light sedation should be provided whenever it is clinically feasible to do so, there is, however, no consideration of the early phase of critical illness. Additionally, no consideration is given to sedation targets in the first 48 hours following mechanical ventilation.

Recent reports have suggested that the first 48 hours constitute a critical period to target sedation depth and it has a significant impact on mortality.[13] Nevertheless, many prospective observational studies continued to demonstrate low adherence to target sedation depth within the first 48 hours.[6,14]

Fourth: Use of Sedatives with Analgesics is Not Considered

The recommendations in the PADIS guidelines were informed by randomised clinical trials (RCT), and most of them had compared the use of 1 agent against another. In contrast, clinicians often use multiple agents and these are combined with opioids that are administered through different routes and in various concentrations.

Although the benefit that accrues from the use of a combination of different agents at lower doses—rather than 1 agent at a higher dose—has not been examined, it is possible that this intervention may yield a synergistic effect whereby the desirable properties of each agent are harnessed at a lower dose and their harmful effects—seen at a higher dose—are minimised.

Strategies to Improve Sedation-Related Outcomes

Early Light Sedation

In the last decade, most sedation RCT involved patients who were on mechanical ventilation for between 48–96 hours. However, sedation depth within the first 48 hours in ICU had an impact on clinical outcomes. A meta-analysis[2] demonstrated lower mortality with an odds ratio (OR) of 0.34, fewer days of mechanical ventilation (−2.07 days) and shorter length of stay (LOS) in ICU (−2.98 days) for early light sedation. Hospital LOS was shorter by 5.9 days and delirium frequency was almost halved with light sedation (OR 0.5), although the results were not statistically significant.

The findings were supported by a large cohort study[3] that showed a positive association between light and moderate sedation levels at day 2 of ICU admission and reduced hospital mortality (OR 0.63), ICU mortality (45.8% vs 57.0%) and ICU LOS (11 vs 12 days). These findings emphasised the importance to achieve targeted light sedation on admission to ICU.

Time-Weighted vs Point-Based Sedation Monitoring

The Sedation Index (SI) or sedation intensity score is derived by dividing the positive sum of aggregate negative RASS scores by the total number of measurements over time. SI has been suggested as a tool that can be used to perform continuous measurement of sedation depth.[3] A low score on SI indicates lighter sedation and provides a measurement of the overall sedation scores of patients over a certain period of time.

SI is shown to have an independent, dose-dependent association with survival at 180 days, time to extubation and subsequent delirium. An increase of 1 point in SI increases the risk of death by nearly 30%, risk of delirium by 25% and time to extubation by 24 hours. SI readings suggest that light sedation should be close to a RASS score of 0 or −1 at most.

The duration of light sedation is important and patients should be lightly sedated continuously from the time of ICU admission. Although this measure of sedation may not be practical in sedative titration to a target, it does, however, underscores the need for continuous and objective measurement of sedation depth. Additionally, it may offer a benchmark in sedation research.

Goal-Directed vs Daily Interruption

Since the 1990s, nurse-led protocols have demonstrated a decrease in the duration of mechanical ventilation and

ICU LOS.[16] A decrease in the dose of sedatives used was also found.[17] Daily awakening trials have shown benefit in studies performed in small centres.[18,19] In the Awakening and Breathing Controlled (ABC) trial,[20] spontaneous awakening trials were paired with spontaneous breathing trials. The findings of the study revealed that the intervention group experienced more days breathing without assistance (3.1 days) and earlier discharge from ICU (9.1 vs 12.9 days) and hospital (14.9 vs 19.2 days). Patients in the intervention group were also less likely to die at the end of the first year (hazards ratio [HR] 0.68, number needed to treat 7.4).

In their study, however, Mehta et al[21] demonstrated that the addition of daily sedation interruption to a standard goal-directed sedation protocol did not reduce the duration of mechanical ventilation or ICU stay. Interestingly, the daily interruptions group received higher doses of benzodiazepines and opioids, and a greater number of boluses were also required to achieve adequate sedation. Since the study used a significant amount of benzodiazepines, the results could be vastly different had the investigators used a benzodiazepine-free sedation strategy instead.

Opioid-Based Sedation vs "No Sedation" Strategy

Since daily interruptions could increase the amount of sedatives used and nursing interventions needed, the way forward would be total avoidance of the use of sedative agents. In 2010, a single-centre Danish study[4] randomised patients to a no-sedation arm (but with analgesic treatment) and a sedation arm with a daily wake-up trial. Patients who did not receive sedation were shown to have had more days without ventilation (4.2 days), shorter ICU LOS (HR 1.86) and hospital LOS (HR 3.57); there was no difference in the incidence of accidental extubations. However, an increase in the incidence of delirium (20% vs 7%) was seen. Since the study used criteria from the 4th Edition of the Diagnostic and Statistical Manual of Mental Disorders—which detects hyperactive delirium—instead of the Confusion Assessment Method for ICU (CAM-ICU), hypoactive delirium could have been underdiagnosed in the control group.

Additionally, the study involved a switch from the use of propofol to midazolam after 48 hours and the use of benzodiazepines, both of which could have confounded the study outcome. Patients in the no-sedation arm also received morphine boluses with a sedative effect and were not titrated to a pain scale. The lack of adequate staff could hinder the use of a no-sedation strategy since another person was needed to comfort 11 patients who were not sedated against 3 patients who were sedated.

In the more recent multicenter NONSEDA trial,[23] no difference was found in 90-day mortality or secondary outcomes—including ventilator-free days and ICU-free days—between the no-sedation arm and light sedation group. In septic post-abdominal surgical patients,[24] a reduction in time to successful extubation (adjusted HR 5.2) and an increase in delirium and coma-free days were found after sedation was ceased immediately upon admission to ICU.

Multimodal Sedation

Several sedatives are currently available, but each of them offers different benefits and harmful side effects. Although an ideal sedative is lacking, the use of a combination of different sedatives at low doses can allow the benefit of each agent to be harnessed and to minimise its side effects. Consequently, patients will feel more comfortable, awake and free from delirium.

Midazolam was highly favoured for its reliability and amnesiac properties. However, the undesirable side effects associated with its use included relatively slow offset and accumulation in organ failure. Consequently, the PADIS guidelines no longer recommended its use since it may lead to increased risks of delirium and longer duration on mechanical ventilation.[8,9]

Propofol, on the other hand, is increasingly being used since it offers better efficacy, rapid onset and offset and ease in titratability. Nevertheless, it can induce significant vasodilatory and negative inotropic effects[25] when it is used in high doses or in severely shocked patients.

Dexmedetomidine increases cooperativeness and effective communication,[8] lowers the incidence of delirium[26,27] and accelerates resolution of delirium.[28] It is also less easily titratable with slower onset than other sedatives. Additionally, it is known to produce bradycardia and hypotension. More insight on the efficacy and side effects of this sedative will be known after the results of the ongoing MENDS II trial—a multicenter, double-blind RCT that compares days alive without delirium or coma in the first 14 days in patients sedated with dexmedetomidine and propofol—are published.[29]

Opioids are used to manage pain and discomfort in ICU patients. However, they can cause somnolence, gut hypomotility and respiratory depression at higher doses. With a short duration of action, fentanyl is initially more easily titratable than morphine, but it accumulates with prolonged use. Its use is preferred in patients with renal impairment since the active ingredient in morphine, metabolite morphine-6-glucuronide, accumulates in renal impairment.

Remifentanil offers organ-independent metabolism and excellent titratability with almost instantaneous onset and offset. At higher doses, however, it becomes a very potent respiratory depressant and could potentially cause hyperalgesia and haemodynamic instability. There is evidence that remifentanil can reduce duration on mechanical ventilation and ICU LOS.[30,31] Although less commonly used than conventional opioids due to its higher cost, a study in the Netherlands showed that the use of remifentanil led to an overall reduction in total health costs at 28 days (€1494), lower ICU LOS (7.6 days vs 8.5 days) and time on mechanical ventilation (5.0 days vs 6.0 days) than other opioids.[32] A recent meta-analysis of 23 RCT with 1905 patients showed a more modest reduction in duration of mechanical ventilation (mean difference [MD] −1.46 hours), time to extubation after cessation of sedation (MD −1.02 hours) and ICU LOS (MD −0.1 days) without a significant difference in costs.[33]

Antipsychotic agents such as haloperidol have been used to treat delirium and agitation, but have no role in prophylaxis or treatment of hypoactive delirium.[34,35] In a large RCT of 1789 patients in the Netherlands that compared low-dose prophylactic haloperidol to placebos, the REDUCE trial did not find a difference in incidence of undifferentiated delirium (MD 1.5%) or delirium-free and coma-free days (MD 0 days).[36] In their study of the treatment of delirium in patients on haloperidol, ziprasidone and placebos, the MIND-USA trial did not find a difference in duration of delirium; however, there was a heavy preponderance of patients with hypoactive delirium.[37] Additionally, both antipsychotic agents precipitated arrhythmias in a patient who had prolonged QTc.[38]

Other atypical antipsychotic agents such as quetiapine have fewer side effects than haloperidol in other clinical settings. A report had demonstrated that quetiapine shortened the duration of delirium, reduced agitation and led to higher rates of discharge back home.[39] Based on current evidence, quetiapine could only be considered for treatment of delirium with agitation or psychotic symptoms.

The dose and number of medications used should be escalated based on patient acuity, underlying pathology and needs of individuals. For example, a patient who is on low-dose opioid infusion to manage pain and discomfort could still receive a regular dose of quetiapine for agitated delirium, low basal infusion of dexmedetomidine to accelerate delirium resolution and readily titratable infusion of propofol to finetune the level of sedation to meet a specified target.

Stepwise Approach to Multimodal Sedation

Based on the preceding discussion on the limitations of existing guidelines and insights from recent trials on strategies to improve sedation-related outcomes, an integrated stepwise approach is proposed to manage sedation or delirium in ICU patients (Fig. 1).

Upon admission to ICU, care should begin with assessment and multimodal management of pain that may include an opioid (intermittent boluses or infusion). After adequate analgesia is achieved, the need for therapeutic sedation should be evaluated and, when indicated, sedative agents with a therapeutic effect for the clinical condition can be started.

As an example, for exceptional circumstances such as when a patient presents with intracranial hypertension, a barbiturate may be administered. In another example, when a patient presents with status epilepticus, a benzodiazepine may be given to control the seizure. When more sedatives are required, propofol and dexmedetomidine may be added, individually or in combination, to achieve the sedation target indicated by the clinical condition.

When sedation is not clinically indicated, the current sedation regime of a patient should be reviewed. For example, when a patient has a RASS score ≤−2, any benzodiazepines that are in use should be ceased immediately, the current sedative dose reduced or a low dose of an alternative agent initiated to aid weaning until the RASS score reaches between 0 to −1. When patients are agitated (RASS ≥2) and are at risk of harming themselves or others, a sedative that addresses delirium—such as dexmedetomidine—should be initiated; when the delirium is hyperactive, quetiapine can be given. Propofol is useful for immediate control, but should be weaned as soon as it is safe to do so. Non-pharmacological measures that address delirium should be undertaken concurrently. When patients are calm and awake (RASS 0 to −1), delirium screening should be performed and when present, treated appropriately.

Delirium-Sparing Strategies

Many of the strategies that improve sedation-related outcomes have also been shown to reduce delirium burden. Analgesic requirements should be titrated in a timely fashion with the use of simple bedside tools such as the Visual Acuity Score in interactive patients[40] or Critical Pain Observation Tool in those who are heavily sedated or are not able to report pain.[41] Early consideration of analgesic adjuncts—such as low-dose ketamine—may decrease delirium rates (21% vs 37%) and duration (2.8 days vs 5.3 days).[42]

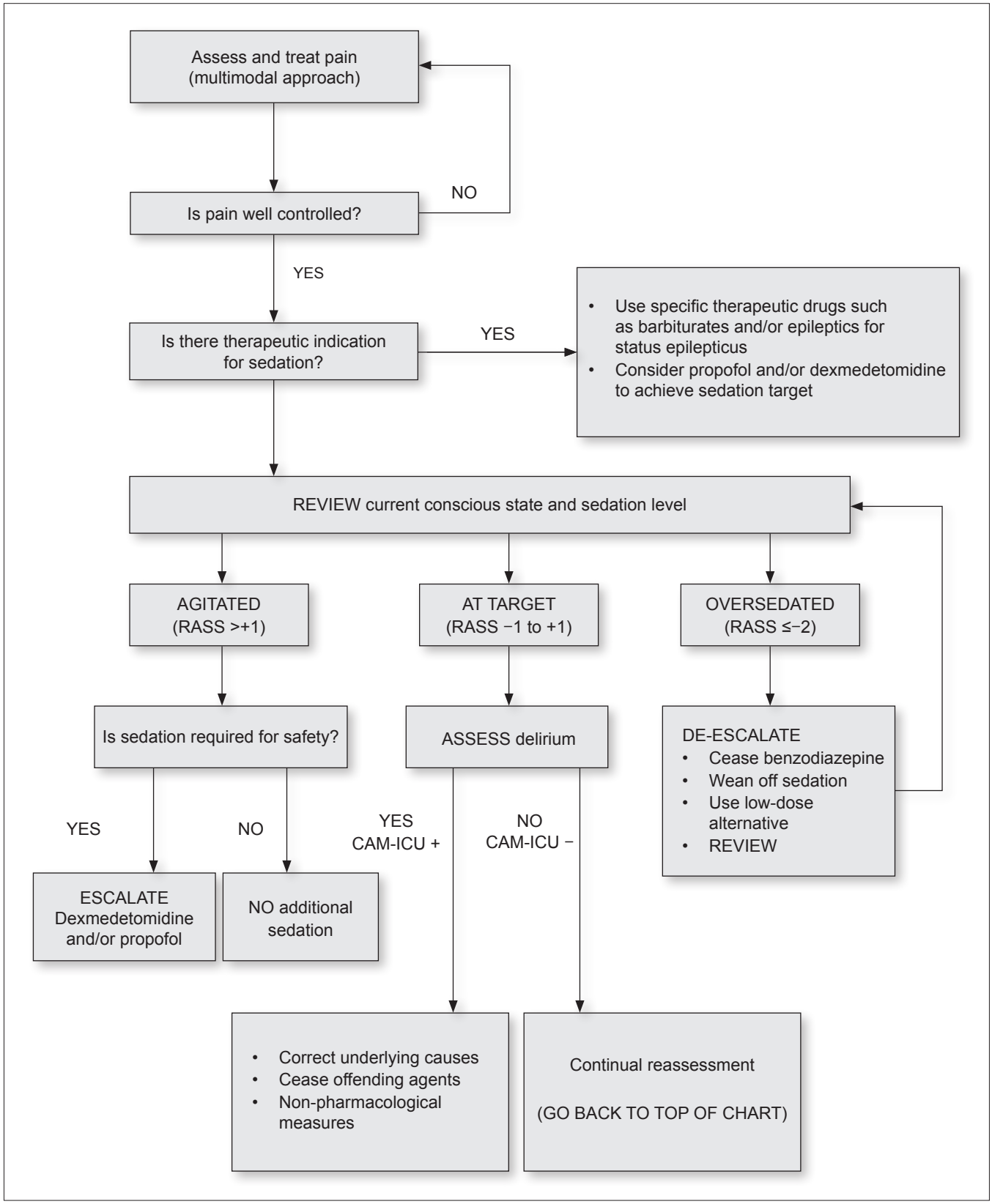

Fig. 1. An integrated stepwise approach to multimodal sedation. There are 5 steps in the model: 1) assess, recognise and treat pain with multimodal analgesia; 2) assess need for sedation; 3) assess current level of sedation and escalate, de-escalate or adjust choice of sedatives to achieve light sedation; 4) assess, recognise and treat delirium; and 5) continual reassessment. CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; RASS: Richmond Agitation and Sedation Scale

By targeting light sedation, patient engagement, early mobilisation and daily delirium screening can result and these outcomes can, in turn, ensure early intervention for delirium through pharmacological and non-pharmacological means. Dexmedetomidine alone, or as part of a multimodal approach, is favoured for its delirium-sparing effect in critical care and perioperative care.[4,27,43–5] Nocturnal use of dexmedetomidine has also shown decreased delirium rates and duration without affecting sleep quality.[46]

Non-pharmacological management strategies such as day-night routines, noise reduction and patient reorientation and refamiliarisation programmes are frequently instituted as part of algorithms to reduce delirium in critical care. Though reasonable in practice, these strategies lack evidence that can help to determine their effect, if any, on delirium duration or incidence.[47]

Sedation Strategy as Part of ICU Bundle

A framework that outlined early implementation of patient-centred care and comfort in ICU is early Comfort using Analgesia, minimal Sedatives and maximal Humane care (eCASH). The emphasis of eCASH is on the use of analgesia first with minimal or no sedation, communication aids, noise reduction to facilitate good sleep, early mobilisation and family involvement.[48]

Another framework is the ICU Liberation Bundle, which is an example of the implementation of the PADIS guidelines as a model that guides early regular assessment and intervention by bedside clinicians. The bundle encompasses the elements of Awakening and Breathing coordination, Choice of drugs, Delirium monitoring and management, Early mobility and Family engagement (ABCDEF). The programme is designed to reduce delirium and improve pain management and long-term consequences in critically ill adults. Studies have shown that adherence to even a part of the ABCDEF bundle could lead to an improvement in patient-centric outcomes.

The findings of the ICU Liberation Collaborative[49] had shown a dose-dependent relationship between compliance and hospital death within 7 days (adjusted HR 0.32), next-day mechanical ventilation (adjusted OR [AOR] 0.28), coma (AOR 0.35), delirium (AOR 0.6), use of physical restraint (AOR 0.37), ICU readmission (AOR 0.54) and discharge to a facility other than home (AOR 0.64). Another multicentre study[50] found an improvement of 7% in hospital survival and increase of 2% in days alive; for every increase of 10% in total bundle compliance, the incidence of delirium and coma is greatly reduced. In New York, the implementation of a full ICU bundle reduced total ICU and hospital cost by 24.2% and 30.2%, respectively, compared to a partial ICU bundle.[51] Trogrlić et al[52] also found that improved mortality and ICU LOS were more statistically likely when ≥6 strategies that targeted delirium assessment, prevention and treatment were used.

In Australia, a quality improvement programme, Victorian Pain Agitation and Delirium, was recently developed as an algorithm for the assessment of pain, targeted sedation and delirium screening. The programme involved prescription of a RASS target twice daily, pain assessment and management at 4-hour intervals and CAM-ICU once daily.[53] Findings from a regular audit of the programme showed that over a 3-month period, compliance improved to >80%. The programme was sustained and maintained through ongoing audit and education. Additionally, it emphasised the need for optimal sedation and delirium prevention in ICU patients.

Consequently, a multipronged approach for optimal sedation-related outcomes (Fig. 2) in ICU patients should involve the collective use of various strategies that include an adherence to the basic premise of the PADIS guidelines with analgesia first, light sedation, multimodal sedation and analgesia, promotion of early mobility and prevention of delirium through pharmacologic and non-pharmacologic means.

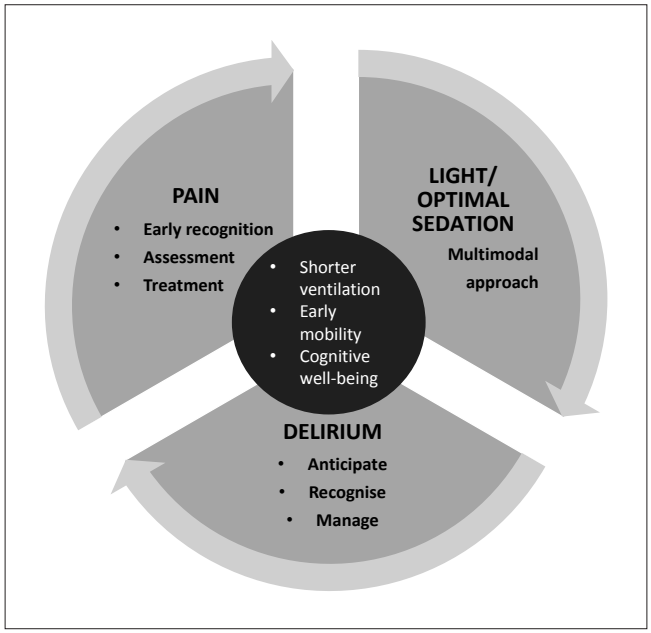

Fig. 2. A multipronged approach to optimal sedation in the Intensive Care Unit.

Practice of Analgesia, Sedation and Delirium Management in Singapore ICU

In the last decade, the practice of analgesia, sedation and delirium in Singapore has changed to conform to the PADIS guidelines. Findings from 3 local studies that described sedation and delirium in ICU[54–6] throughout the city-state are shown in Table 2. In particular, the study by Lee et al[56] is a subgroup analysis of the SPICE cohort in Singapore.[55]

In summary, sedation use in Singapore ICU ranged from between 25.8–70.3%; the use of fentanyl and propofol also predominated. Benzodiazepine use was

Table 2. Comparison of Major Findings from 3 Studies on Sedation Practices in Singapore

Variable	Koh et al*	Ng et al†	Lee et al‡
Type	Point-prevalence survey	Prospective, observational cohort	Prospective, observational cohort
Year	2008	2012	2012
Number of hospitals	5	4	1
Number of ICU	11	7	2
Number of cases	93	198	58
Sedation in ICU, %	25.8	70.3	52.4
Sedation scale usage, %	75	100	100
Choice of sedative, %			
Propofol	50	36	44.2
Morphine/fentanyl	Not reported	56.8	33.8
Midazolam	41.7	11.4	6.7
Sedation target prescribed, %	20.8	38.7	11.1
Light sedation, %			
Total	NA	79.3	79.1
Early period in ICU stay		70	64.8
Subsequent period in ICU		83	84.7
Use of physical restraints, %	29	55.5	NA
Delirium assessment			
Method	Clinical judgement	CAM-ICU	CAM-ICU
Compliance to assessment, %	NA	76	NA
Delirium incidence	NA	23.7	22.4
Difference between MICU/SICU practices	Yes	NA	Yes
Major differences in SICU	• More propofol and less midazolam use • Frequent sedation assessments		• More sedation targets and prescriptions • Less midazolam use • Lower sedation dose • More patients in light sedation range • Lower delirium incidence

CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; ICU: Intensive Care Unit; MICU: Medical Intensive Care Unit; NA: Not applicable; SICU: Surgical Intensive Care Unit

*Koh J, Tee A, Phoo JWH, et al. A national point-prevalence survey of the use of sedation, analgesia, neuromuscular blockade and delirium assessment in adult intensive care units in Singapore. Intensive Care Med 2009;4:S64.

†Ng SY, Phua J, Wong YL, Kalyanasundaram G, Mukhopadhyay A, Lim D, et al. Singapore SPICE: sedation practices in intensive care evaluation in Singapore—a prospective cohort study of the public healthcare system. Singapore Med J 2020;61:19–23.

‡Lee YL, Kalyanasundaram G, Ti LK, Ng SY. A prospective, observational, longitudinal cohort study of sedation practices in SGH intensive care units. Proc Singapore Healthc 2018;27:103–9.

mostly restricted to midazolam in patients involved in the studies, but the use of midazolam became uncommon in later studies (dropping from 41.7% in 2008 to 11.4% in 2012). Most patients were lightly sedated from the start of ICU admission.

Initially, delirium screening was rarely done; however, it became common in later studies despite the contextual and linguistic challenges faced in adapting CAM-ICU for use in local practice. Overall, the incidence of delirium in Singapore ICU is low and could be attributed to the predominant use of analgesics such as fentanyl, low use of midazolam and practice of light sedation. Additionally, efforts were made to improve delirium screening in ICU through nurse-led education initiatives.[57] Baseline compliance is high for sedation monitoring, but low for delirium screening. A comprehensive education programme that comprised didactics, patient simulation and beside-proctored interaction with real patients resulted in sustained improvement in compliance to delirium screening from 36% at baseline to 61% at 10 months.[57]

Future directions for sedation, agitation and delirium research in Singapore could include identification of unique cultural beliefs or factors that aid local sedation practices and overcoming those that are harmful. An understanding of the evolution of local sedation practices over the last decade would also be beneficial to identify areas that need more emphasis. Further research could be performed on compliance to implementation of ICU care bundles such as the ABCDEF programme and other non-pharmacological methods to improve sedation and delirium-related, patient-centred outcomes. Assessment of non-pharmacologic strategies that are unique to Singapore is needed (such as a supportive family who is given access during ICU stay, availability of technology for patients to communicate and interact and for recreation/reorientation). Since sedation strategies currently recommend light to no sedation where possible, it is important to determine post ICU patient-centred outcomes—cognitive function, physical recovery, post-traumatic stress disorder, anxiety and depression, return to former quality of life—and burden of ICU care in an ageing population.

Conclusion

A multipronged approach to optimal sedation leads to improved patient outcomes in ICU. The importance of targeting light sedation early in the acute phase of critical illness and its impact on mortality, delirium and long-term outcomes must be emphasised. More effort must be devoted to the creation of a sedation scoring system that is both practical and time-weighted. A bundled approach that adheres to analgesia first with no sedation or the practice of balanced, multimodal sedation—when necessary—is essential to help patients remain alert, cooperative and delirium-free as well as to lower their mortality and duration of mechanical ventilation, facilitate early mobilisation and increase cognitive well-being.

REFERENCES

1. Rowe K, Fletcher S. Sedation in the intensive care unit. Contin Educ Anaesth Crit Care Pain 2008;8:50–5.
2. Cohen D, Horiuchi K, Kemper M, Weissman C. Modulating effects of propofol on metabolic and cardiopulmonary responses to stressful intensive care unit procedures. Crit Care Med 1996;24:612–7.
3. Shehabi Y, Bellomo R, Kadiman S, Ti LK, Howe B, Reade MC, et al. Sedation intensity in the first 48 hours of mechanical ventilation and 180-day mortality: a multinational prospective longitudinal cohort study. Crit Care Med 2018;46:850–9.
4. Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, et al. Early goal-directed sedation versus standard sedation in mechanically ventilated critically III patients: a pilot study. Crit Care Med 2013;41:1983–91.
5. Liu X, Xie G, Zhang K, Song S, Song F, Jin Y, et al. Dexmedetomidine vs propofol sedation reduces delirium in patients after cardiac surgery: a meta-analysis with trial sequential analysis of randomized controlled trials. J Crit Care 2017;38:190–6.
6. Nassar Jr AP, Zampieri FG, Salluh JI, Bozza FA, Machado FR, Guimarães HP, et al. Organizational factors associated with target sedation on the first 48 h of mechanical ventilation: an analysis of checklist-ICU database. Crit Care 2019;23:34.
7. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018;46:e825–73.
8. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 2012;307:1151–60.
9. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301:489–99.
10. Deol H, Minaie A, Surani S, Udeani G. P243 reliability and utility of the Ramsay sedation scale for dosing sedatives in critically ill intubated patients. Chest 2017;151:A143.
11. Deol HS, Surani SR, Udeani G. Inter-rater reliability of the Ramsay sedation scale for critically-ill intubated patients. Cureus 2019;11:e6021.
12. Barbato M, Barclay G, Potter J, Yeo W, Chung J. Correlation between observational scales of sedation and comfort and bispectral index scores. J Pain Symptom Manage 2017;54:186–93.
13. Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. Am J Respir Crit Care Med 2012; 186:724–31.
14. Aragón RE, Proaño A, Mongilardi N, de Ferrari A, Herrera P, Roldan R, et al. Sedation practices and clinical outcomes in mechanically ventilated patients in a prospective multicenter cohort. Crit Care 2019;23:130.

15. Stephens RJ, Dettmer MR, Roberts BW, Ablordeppey E, Fowler SA, Kollef MH, et al. Practice patterns and outcomes associated with early sedation depth in mechanically ventilated patients: a systematic review and meta-analysis. Crit Care Med 2018;46:471–9.
16. Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 1999;27:2609–15.
17. Abdar ME, Rafiei H, Abbaszade A, Hosseinrezaei H, Abdar ZE, Delaram M, et al. Effects of nurses' practice of a sedation protocol on sedation and consciousness levels of patients on mechanical ventilation. Iran J Nurs Midwifery Res 2013;18:391–5.
18. Hughes CG, Girard TD, Pandharipande PP. Daily sedation interruption versus targeted light sedation strategies in ICU patients. Crit Care Med 2013;41:S39–45.
19. Nassar Jr AP, Park M. Daily sedative interruption versus intermittent sedation in mechanically ventilated critically ill patients: a randomized trial. Ann Intensive Care 2014;4:14.
20. Girard TD, Kress JP, Fuchs BD, Thomason JWW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled Trial): a randomised controlled trial. Lancet 2008;371:126–34.
21. Mehta S, Burry L, Cook D, Fergusson D, Steinberg M, Granton J, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA 2012;308:1985–92.
22. Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet 2010;375:475–80.
23. Olsen HT, Nedergaard HK, Strøm T, Oxlund J, Wian K, Ytrebø LM, et al. Nonsedation or light sedation in critically ill, mechanically ventilated patients. N Engl J Med 2020;382:1103–11.
24. Chanques G, Conseil M, Roger C, Constantin J, Prades A, Carr J, et al. Immediate interruption of sedation compared with usual sedation care in critically ill postoperative patients (SOS-ventilation): a randomised, parallel-group clinical trial. Lancet Respir Med 2017;5:795–805.
25. Lee TL. Pharmacology of propofol. Ann Acad Med Singapore 1991;20:61–5.
26. Kawazoe Y, Miyamoto K, Morimoto T, Yamamoto T, Fuke A, Hashimoto A, et al. Effect of dexmedetomidine on mortality and ventilator-free days in patients requiring mechanical ventilation with sepsis a randomized clinical trial. JAMA 2017;317:1321–8.
27. Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE, et al. Early sedation with dexmedetomidine in critically ill patients. N Engl J Med 2019;380:2506–17.
28. Reade MC, Eastwood GM, Bellomo R, Bailey M, Bersten A, Cheung B, et al. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. JAMA 2016;315:1460–8.
29. Pandharipande P. Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Septic Patients With Acute Respiratory Failure (MENDS2). Available at: https://clinicaltrials.gov/ct2/show/NCT01739933. Accessed on 19 March 2020.
30. Wilhelm W, Kreuer S. The place for short-acting opioids: special emphasis on remifentanil. Crit Care 2008;12:S5.
31. Futier E, Chanques G, Constantin SC, Vernis L, Barres A, Guerin R, et al. Influence of opioid choice on mechanical ventilation duration and ICU length of stay. Minerva Anestesiol 2012;78:46–53.
32. Al MJ, Hakkaart L, Tan SS, Bakker J. Cost-consequence analysis of remifentanil-based analgo-sedation vs. conventional analgesia and sedation for patients on mechanical ventilation in the Netherlands. Crit Care 2010;14:R195.
33. Zhu Y, Wang Y, Du B, Xi X. Could remifentanil reduce duration of mechanical ventilation in comparison with other opioids for mechanically ventilated patients? A systematic review and meta-analysis. Crit Care 2017;21:206.
34. Oh ES, Needham DM, Nikooie R, Wilson LM, Zhang A, Robinson KA, et al. Antipsychotics for preventing delirium in hospitalized adults: a systematic review. Ann Intern Med 2019;doi:10.7326/M19-1859.
35. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: a systematic review and meta-analysis. J Am Geriatr Soc 2016;64:705–14.
36. Van Den Boogaard M, Slooter AJC, Brüggemann RJM, Schoonhoven L, Beishuizen A, Vermeijden JW, et al. Effect of haloperidol on survival among critically ill adults with a high risk of delirium: the REDUCE randomized clinical trial. JAMA 2018;319:680–90.
37. Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, et al. Haloperidol and ziprasidone for treatment of delirium in critical illness. N Engl J Med 2018;379:2506–16.
38. Markowitz JD, Narasimhan M. Delirium and antipsychotics: a systematic review of epidemiology and somatic treatment options. Psychiatry (Edgmont) 2008;5:29–36.
39. Devlin JW, Roberts RJ, Fong JJ, Skrobik Y, Riker RR, Hill NS, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med 2010;38:419–27.
40. Klein C, Caumo W, Gélinas C, Patines V, Pilger T, Lopes A, et al. Validation of two pain assessment tools using a standardized nociceptive stimulation in critically ill adults. J Pain Symptom Manage 2018;56:594–601.
41. Gélinas C, Arbour C, Michaud C, Vaillant F, Desjardins S. Implementation of the critical-care pain observation tool on pain assessment/management nursing practices in an intensive care unit with nonverbal critically ill adults: a before and after study. Int J Nurs Stud 2011;48:1495–504.
42. Perbet S, Verdonk F, Godet T, Jabaudon M, Chartier C, Cayot S, et al. Low doses of ketamine reduce delirium but not opiate consumption in mechanically ventilated and sedated ICU patients: a randomised double-blind control trial. Anaesth Crit Care Pain Med 2018;37:589–95.
43. Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet 2016;388:1893–1902.
44. Huyan T, Hu X, Peng H, Zhu Z, Li Q, Zhang W. Perioperative dexmedetomidine reduces delirium in elderly patients after lung cancer surgery. Psychiatr Danub 2019;31:95–101.
45. Liu X, Xie G, Zhang K, Song S, Song F, Jin Y, et al. Dexmedetomidine vs propofol sedation reduces delirium in patients after cardiac surgery: a meta-analysis with trial sequential analysis of randomized controlled trials. J Crit Care 2017;38:190–6.

46. Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-dose nocturnal dexmedetomidine prevents ICU delirium. A randomized, placebo-controlled trial. Am J Respir Crit Care Med 2018; 197:1147–56.

47. Herling SF, Greve IE, Vasilevskis EE, Egerod I, Mortensen CB, Møller AM, et al. Interventions for preventing intensive care unit delirium in adults. Cochrane database Syst Rev 2018;11:CD009783.

48. Vincent J, Shehabi Y, Walsh TS, Pandharipande P, Ball JA, Spronk P, et al. Comfort and patient-centred care without excessive sedation: the eCASH concept. Intensive Care Med 2016;42:962–71.

49. Pun BT, Balas MC, Barnes-Daly MA, Thompson JL, Aldrich JM, Barr J, et al. Caring for critically ill patients with the ABCDEF bundle: results of the ICU Liberation Collaborative in over 15,000 adults. Crit Care Med 2019;47:3–14.

50. Barnes-Daly MA, Phillips G, Ely EW. Improving hospital survival and reducing brain dysfunction at seven California community hospitals: implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. Crit Care Med 2017;45:171–8.

51. Hsieh SJ, Otusanya O, Gershengorn HB, Hope AA, Dayton C, Levi D, et al. Staged implementation of awakening and breathing, coordination, delirium monitoring and management, and early mobilization bundle improves patient outcomes and reduces hospital costs. Crit Care Med 2019;47:885–93.

52. Trogrlić Z, van der Jagt M, Bakker J, Balas MC, Ely EW, van der Voort PHJ, et al. A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes. Crit Care 2015;19:157.

53. Breheny C. Intensive care pain, agitation and delirium standardised assessment and monitoring. Available at: https://www.bettersafercare.vic.gov.au/critical-care-network/pain-agitiation-delirium-standardised-guidelines. Accessed on 19 December 2019.

54. Koh J, Tee A, Phoo JWH, et al. A national point-prevalence survey of the use of sedation, analgesia, neuromuscular blockade and delirium assessment in adult intensive care units in Singapore. Intensive Care Med 2009;4:S64.

55. Ng SY, Phua J, Wong YL, Kalyanasundaram G, Mukhopadhyay A, Lim D, et al. Singapore SPICE: sedation practices in intensive care evaluation in Singapore—a prospective cohort study of the public healthcare system. Singapore Med J 2020;61:19–23.

56. Lee YL, Kalyanasundaram G, Ti LK, Ng SY. A prospective, observational, longitudinal cohort study of sedation practices in SGH intensive care units. Proc Singapore Healthc 2018;27:103–9.

57. Lieow JLM, Chen FSM, Song G, Tang PS, Kowitlawakul Y, Mukhopadhyay A. Effectiveness of an advanced practice nurse-led delirium education and training programme. Int Nurs Rev 2019;66:506–13.

Review Article

Emerging Treatment Options for Migraine

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Abstract

Migraine is one of top 5 medical conditions that contribute to Years Lived with Disability and affects approximately 1 billion people from around the world. To date, preventive treatment and acute therapies for migraine are limited, have undesirable side effects and are poorly tolerated in patients. In the last few decades, considerable advances in our understanding of migraine and its pathophysiology have paved the way for the development of targeted treatment options. Calcitonin gene-related peptide (CGRP) plays an integral role in the neurobiology of migraine, and new classes of drugs that target the CGRP pathway have included gepants and CGRP pathway monoclonal antibodies. Serotonin 5-HT_{1F} receptor agonists—namely ditans—have also been developed to treat acute migraine. Lastly, non-invasive neuromodulation offers another treatment option for migraine patients who prefer treatments that have fewer side effects and are well tolerated. In this review, we discussed emerging treatment options for migraine that were made available in recent years.

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Key words: Calcitonin gene-related peptide monoclonal antibody, Gepants, Headache, Lasmiditan, Neuromodulation

Introduction

As 1 of the top 5 medical conditions that contribute to Years Lived with Disability,[1] migraine is estimated to affect 1 billion individuals from around the world. Despite the high cumulative lifetime risk that migraine poses to many people,[2] preventive treatment of the condition is still limited.

Currently, acute treatment options for migraine include analgesics such as acetaminophen, aspirin and non-steroidal anti-inflammatory drugs. These treatments are non-targeted and are associated with significant side effects.[3] Ergotamine preparations have been used for close to 100 years but are no longer considered good treatment option due to the many side effects associated with their use.[4] Triptans, which are serotonin 5-$HT_{1B/1D}$ receptor agonists,[5] were the first group of drugs that were specifically designed to treat migraine.[6] Triptans have important limitations, especially contraindications in patients with cardiovascular risk factors.[7]

Preventive medications for migraine faced similar problems. Conventional treatment options were

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serendipitously borrowed from treatments of other conditions that were not specifically developed to treat migraine. Consequently, the wide range of mechanisms of action had led to undesirable side effects. These factors undermined the efficacy of the drugs that were attributed to poor tolerability and resulted in poor adherence and persistence in patients.[8,9] Studies have shown that up to 80% of patients discontinued their preventive migraine treatments within 1 year after they were started on them.[10]

The unmet needs and challenges faced by migraine patients and medical practitioners alike have led to a search for new treatment options. In the last few decades, considerable advances were made in our understanding of migraine and its pathophysiology,[11,12] and they helped to pave the way for the development of targeted treatment options such as calcitonin gene-related peptide (CGRP) that targets the neurobiology of migraine.[11] The new classes of drugs that were developed specifically target the CGRP pathway and included small-molecule CGRP receptor antagonists or gepants and CGRP monoclonal antibodies.[13,14] Both classes of drugs have emerged as frontrunners in acute and preventive treatment of migraine, respectively.

Non-triptan serotonergic agonists that have better cardiovascular safety profile—namely serotonin 5-HT_{1F} receptor agonists or ditans—were also developed.[15] Additionally, non-invasive neuromodulation is a useful treatment in migraine patients who prefer treatments that offer fewer side effects and tolerability issues[16] or have contraindications to existing pharmacological options. In this review, we focus on emerging therapeutic options for acute treatment and prevention of migraine.

Emerging Preventive Therapies

CGRP Pathway Monoclonal Antibodies

CGRP monoclonal antibodies were developed for preventive treatment of migraine. The early success of onabotulinumtoxin A in the prevention of chronic migraine suggested that peripheral drugs were effective as migraine therapy.[17] However, the site of action of onabotulinumtoxin A in migraine remains unresolved. Since CGRP monoclonal antibodies have large molecular weight, it is postulated that they do not cross the blood-brain barrier substantially. Consequently, they are assumed to exert only a peripheral effect on the trigeminovascular structures.

As a class of drugs, CGRP monoclonal antibodies target either the CGRP receptor or its ligand. Hence, there are minimal unintended side effects with vastly improved tolerability. Additionally, their long half-lives make them ideal for dosing at longer intervals and obviate the need for daily dosing.[14]

Recently, 4 monoclonal antibodies—erenumab, fremanezumab, galcanezumab and eptinezumab—were developed and approved by the Unites States Food and Drug Administration (FDA) in the last 2 years (Table 1).[18–20] Erenumab was the first monoclonal

Table 1. Summary of CGRP Monoclonal Antibodies

CGRP Monoclonal Antibody	Route of Administration	Target	Molecular Form	Recommended Dose and Frequency	Main Adverse Reactions
Eptinezumab (ALD-403)*	Intravenous	CGRP ligand	Humanised IgG1	100 mg or 300 mg every 3 months	Flu-like symptoms, fatigue, nausea/vomiting
Erenumab (AMG-334)†	Subcutaneous	CGRP receptor	Human IgG2	70 mg or 140 mg every month	Injection site reaction, flu-like symptoms, constipation
Fremanezumab (TEV-48125)‡	Subcutaneous	CGRP ligand	Humanised antiCGRP IgG2	225 mg every month or 675 mg every 3 months	Injection site reaction, pruritus
Galcanezumab (LY-2951742)§	Subcutaneous	CGRP ligand	Humanised antiCGRP IgG4	240 mg loading and 120 mg every month thereafter	Injection site reaction, flu-like symptoms, abdominal pain

CGRP: Calcitonin gene-related peptide; IgG1: Immunoglobulin G1; IgG2: Immunoglobulin G2; IgG4: Immunoglobulin G4

*Lipton R. Eptinezumab for Prevention of Chronic Migraine: Results of 2 Quarterly Intravenous Infusions in the Phase 3 PROMISE-2 (Prevention Of Migraine via Intravenous eptinezumab Safety and Efficacy-2) Trial. Scientific Presentation at the American Headache Society Annual Meeting, 28 June–1 July 2018, San Francisco, CA, USA.

†Shi L, Lehto SG, Zhu DXD, Sun H, Zhang J, Smith BP, et al. Pharmacologic characterization of AMG334, a potent and selective human monoclonal antibody against the calcitonin gene-related peptide receptor. J Pharmacol Exp Ther 2016;356:223–31.

‡Bigal ME, Escandon R, Bronson M, Walter S, Sudworth M, Huggins JP, et al. Safety and tolerability of LBR-101, a humanized monoclonal antibody that blocks the binding of CGRP to its receptor: results of the phase 1 program. Cephalalgia 2014;34:483–92.

§Benschop RJ, Collins EC, Darling RJ, Allan BW, Leung D, Conner EM, et al. Development of a novel antibody to calcitonin gene-related peptide for the treatment of osteoarthritis-related pain. Osteoarthritis Cartilage 2014;22:578–85.

antibody that was approved for use by the FDA in May 2018 (Table 2).[18]

Erenumab (AMG-334)

Erenumab differs from the other 3 monoclonal antibodies in that it is a fully human antibody and targets the canonical CGRP receptor, the calcitonin-like receptor/RAMP 1 complex.[21] Erenumab is available in several countries since 2018.[18] Results from initial phase 2 trials showed that it has good safety and tolerability profile in the treatment of chronic and episodic migraines.[22,23] In episodic migraine, erenumab 70 mg was established as an effective dose in patients of a 5-year open-label extension study. An interim study published in 2017 also demonstrated favourable safety and tolerability profiles, including improved measurements across the primary and secondary endpoints.[24]

Two large phase 3 trials, ARISE and STRIVE,[25,26] showed success in the primary endpoint of reduction in mean monthly migraine days. In ARISE, 577 patients who experienced episodic migraine were randomised to a placebo group and a treatment group that were given erenumab 70 mg; consequently, a reduction of −2.9 monthly migraine days was seen in the treatment group against −1.8 days in placebos.[25] In STRIVE, 955 patients with episodic migraine were randomised to 3 treatment arms comprising placebos, erenumab 70 mg and 140 mg who were treated for 6 months. Between 4–6 months, mean reduction in monthly migraine days was 3.2 in the 70 mg group, 3.7 in the 140 mg group and 1.8 in placebos. The study also achieved positive results in all secondary endpoints, including a reduction of 50% in mean monthly migraine days and mean number of days of taking acute migraine-specific medications.[26]

In ARISE and STRIVE, patients who failed >2 migraine prevention treatments were excluded. A separate study, LIBERTY, addressed this issue by randomising these patients with episodic migraine to either placebos or erenumab 140 mg. The 50% responder rate for reduction in monthly migraine days was 30% in treated patients and 14% in placebos. This finding supported the efficacy of erenumab in a group of difficult-to-treat migraine patients.[27]

Fremanezumab (TEV-48125)

Fremanezumab is a humanised, subcutaneous immunoglobulin G2 monoclonal antibody that targets the alpha and beta forms of the CGRP ligand.[28] It is the only CGRP monoclonal antibody that offers monthly and quarterly dosing schedules, and was approved by the FDA in September 2018.[19]

In phase 3 of the HALO episodic migraine prevention trial, monthly and quarterly treatments with fremanezumab 225 mg and 675 mg reduced mean monthly migraine days by 3.7 and 3.4 days, respectively, compared to −2.2 days in placebos.[29] In phase 3 of the HALO chronic migraine prevention trial, the results in both treatment arms were also positive compared to placebos.[30] In both trials, injection site reactions were more commonly reported in treated patients than placebos.

Galcanezumab (LY-2951742)

Galcanezumab is one of 2 humanised, subcutaneous monoclonal antibodies that target the CGRP ligand.[31] The results from 2 phase 3 randomised controlled trials, EVOLVE-1 and EVOLVE-2, that examined the effect of galcanezumab 120 mg and 240 mg on episodic migraine[32,33] showed a reduction in mean monthly migraine days with good overall efficacy, safety and tolerability.

For chronic migraine, the REGAIN study also yielded positive results with galcanezumab 120 mg and 240 mg that showed a significant reduction in mean monthly migraine days compared to placebos.[34]

Eptinezumab (ALD-403)

Eptinezumab is a 90% humanised, immunoglobulin G1 subtype monoclonal antibody that targets the CGRP ligand.[35] It was approved by the FDA in February 2020 for preventive migraine treatment in adults.[36] It is the only monoclonal antibody that is administered through infusion. Since it is administered on a quarterly basis, it has the additional advantage of reaching peak concentrations very quickly.[35,37]

Pivotal trials of eptinezumab include 2 phase 3 trials, PROMISE-1 and PROMISE-2, in episodic and chronic migraine, respectively.[38,39] Notably, both trials included a unique secondary outcome measure that scrutinised the probability of a migraine attack happening at day 1 post-infusion. In PROMISE-1, the probability of a migraine attack at day 1 was reduced by 45% to 53.6% in 3 treatment arms compared to 20.7% in placebos.[38] In PROMISE-2, the results were equally encouraging; the likelihood of migraine at day 1 was reduced by 51% and 53% for eptinezumab 100 mg and 300 mg, respectively, compared to 27% in placebos.[39] The quick onset of efficacy will likely confer an additional advantage on eptinezumab by helping it to gain wider use in acute treatment of migraine than other monoclonal antibodies.

Table 2. Key Trials in Calcitonin Gene-Related Peptide (CGRP) Development

CGRP Monoclonal Antibody and Trial	Active Arm Dose and Frequency	Sample Size	Target Population	Treatment Duration	Change in Mean Monthly Headache Days		Treatment Difference (*P* Value)	≥50% Response Rate		*P* Value
					Active	Placebo		Active (%)	Placebo (%)	
Erenumab										
ARISE[*]	70 mg every 4 weeks	577	Episodic migraine	12 weeks	−2.9	−1.8	−1.0 (<0.001)	39.7	29.5	0.010
STRIVE[†]	Arm 1: 70 mg every 4 weeks	955	Episodic migraine	6 months	−3.2	−1.8	−1.4 (<0.001)	43.3	26.6	<0.001
	Arm 2: 140 mg every 4 weeks				−3.7		1.9 (<0.001)	50		<0.001
Fremanezumab										
HALO[‡]	Arm 1: 225 mg every 4 weeks	875	Episodic migraine	12 weeks	−4.0	−2.6	−1.4 (<0.001)	47.7	27.9	<0.001
	Arm 2: 675 mg, single dose				−3.9		−1.3 (<0.001)	44.4		<0.001
HALO II[§]	Arm 1: 675 mg, single dose	1130	Chronic migraine	12 weeks	−4.3	−2.5	−1.8 (<0.001)	38	18	<0.001
	Arm 2: 675 mg at baseline followed by 225 mg at weeks 4 and 8				−4.6		−2.1 (<0.001)	41		<0.001
Galcanezumab										
EVOLVE I[‖]	Arm 1: 120 mg every 4 weeks	858	Episodic migraine	6 months	−4.7	−2.8	−1.9 (<0.001)	62.3	38.6	<0.001
	Arm 2: 240 mg every 4 weeks				−4.6		−1.8 (<0.001)	60.9		<0.001

[*]Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, et al. ARISE: a phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia 2018;38:1026–37.

[†]Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, et al. A controlled trial of erenumab for episodic migraine. N Engl J Med 2017;377:2123–32.

[‡]Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. JAMA 2018;319:1999–2008.

[§]Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med 2017;377:2113–22.

[‖]Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. JAMA Neurol 2018;75:1080–8.

Table 2. Key Trials in Calcitonin Gene-Related Peptide (CGRP) Development (Cont'd)

CGRP Monoclonal Antibody and Trial	Active Arm Dose and Frequency	Sample Size	Target Population	Treatment Duration	Change in Mean Monthly Headache Days		Treatment Difference (*P* Value)	≥50% Response Rate		*P* Value
					Active	Placebo		Active (%)	Placebo (%)	
EVOLVE 2[¶]	Arm 1: 120 mg every 4 weeks	915	Episodic migraine	6 months	−4.3	−2.3	−2.0 (<0.001)	59.3	36	<0.001
	Arm 2: 240 mg every 4 weeks				−4.2		−1.9 (<0.001)	56.5		<0.001
REGAIN[#]	Arm 1: 120 mg monthly with loading dose of 240 mg	1113	Chronic migraine	3 months (9-month open-label extension)	−4.8	−2.7	−2.1	27.6	15.4	<0.001
	Arm 2: 240 mg for 3 months				−4.6		−1.9	27.5		<0.001
Eptinezumab										
PROMISE 1[**]	Arm 1: 30 mg every 4 weeks	888	Episodic migraine	12 weeks	−4.0	−3.2	−0.8 (0.0045)	50.2	37.4	
	Arm 2: 100 mg every 4 weeks				−3.9		−0.7 (0.0179)	49.8		
	Arm 3: 300 mg every 4 weeks				−4.3		−1.1 (0.0001)	56.3		
PROMISE 2[††]	Arm 1: 100 mg every 4 weeks	1022	Chronic migraine	6 months	−7.7	−5.6 (at months 1–3)	−2.1 (<0.0001)	61	44	
	Arm 2: 300 mg every 4 weeks				−8.2 (at months 1–3)		−2.6 (<0.0001)	64		

[¶]Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 phase 3 randomized controlled clinical trial. Cephalalgia 2018;38:1442–54.

[#]Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. Neurology 2018;91:e2211–21.

[**]Saper J, Lipton R, Kudrow D, Hirman J, Dodick D, Silberstein S, et al. Primary results of PROMISE-1 (Prevention Of Migraine via Intravenous eptinezumab Safety and Efficacy–1) trial: a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of eptinezumab for prevention of frequent episodic migraines. Neurology 2018;90:S20.001.

[††]Lipton R. Eptinezumab for Prevention of Chronic Migraine: Results of 2 Quarterly Intravenous Infusions in the Phase 3 PROMISE-2 (Prevention Of Migraine via Intravenous eptinezumab Safety and Efficacy-2) Trial. Scientific Presentation at the American Headache Society Annual Meeting, 28 June–1 July 2018, San Francisco, CA, USA.

Emerging Acute Therapies

5-HT$_{1F}$ Receptor Agonists

Triptans are serotonin 5-HT$_{1B/1D}$ receptor agonists and have remained the mainstay of acute migraine treatment since their introduction.[40] Despite evidence to the contrary,[41] the potential for vasoconstriction associated with their use has curbed their widespread usage over concerns of cardiovascular and cerebrovascular risks.

Ditans are a new class of serotonin 5-HT$_{1F}$ receptor agonists that were developed to treat acute migraine. Lasmiditan was the first medicine to be introduced and approved by the FDA for the acute treatment of migraine with or without aura.[42] Preclinical studies have demonstrated that 5-HT$_{1F}$ receptor agonists can inhibit trigeminocervical nociceptive traffic independent of any vascular effect.[43] Lasmiditan acts by reducing plasma protein extravasation at the trigeminal ganglion.[44] It selectively targets 5-HT$_{1F}$ receptors—which are not expressed in the vasculature[45]—and inhibits trigeminocervical nociceptive transmission. Its expression in the trigeminovascular system provides relief from migraine pain without the vasoconstrictor effects associated with triptans, potentially benefitting migraine patients who have concomitant cardiovascular or cerebrovascular conditions.[46]

A phase 3 placebo-controlled randomised trial, SAMURAI, that investigated lasmiditan 100 mg and 200 mg in acute treatment of migraine found that pain relief at 2 hours was 59% compared to 43% in placebos. Also, 41% of patients experienced relief from their most bothersome symptoms with lasmiditan 100 mg and 200 mg compared to 30% in placebos.[47] Similarly, phase 3 of the SPARTAN trial demonstrated positive results for lasmiditan 50 mg, 100 mg and 200 mg in providing relief from pain at 2 hours and from most bothersome symptoms.[48]

Lasmiditan was generally well tolerated, with paraesthesia and dizziness reported as the most frequent adverse events.[49] This finding was consistent with preliminary results reported in the open-label study, GLADIATOR, which ended recently and the publication of its results are currently pending.[50]

CGRP Receptor Antagonists and Gepants

In the 1990s, a class of serotonin 5-HT$_{1B/1D}$ receptor agonists, the triptans, were introduced as acute therapy in migraine management.[51] However, the potential vasoconstrictor effects associated with their use in patients with cardiovascular and cerebrovascular diseases had prevented their widespread use.[7,52] Studies had shown that CGRP levels were elevated in the jugular vein during spontaneous and provoked migraine attacks. Provocation studies that used CGRP had shown that it could induce migraine-like attacks in migraineurs that subsided after they were given triptans.[53–5] Against this background, interest turned to the development of gepants.

The first proof of concept study drug, BIBN 4096 BS (olcagepant), proved effective in the acute treatment of migraine attacks. Since it was administered intravenously,[56,57] it was never commercialised. Subsequently, gepants were developed as oral medications including BI 44370 TA, telcagepant, MK-3207, rimegepant and ubrogepant. The initial development of this class of drugs was temporarily halted after concerns were raised over the hepatotoxicity of telcagepant and MK-3207.[58,59] Apart from atogepant that was developed as preventive migraine therapy, most trials on gepants focused mainly on acute migraine treatment (Table 3).[13]

Ubrogepant

Ubrogepant has completed 2 positive phase 3 studies (ACHIEVE I and II). In Achieve I, 1327 patients were randomised to placebos, ubrogepant 50 mg and 100 mg.[60] The study met the primary endpoints of relief from pain for 2 hours and absence of most bothersome symptoms for both doses compared to placebos. Achieve II randomised 1355 patients to a lower dose of 25 mg and 50 mg.[61] Both doses showed statistically significant results in providing relief from pain for 2 hours compared to placebos, while the 50 mg dose provided absence of most bothersome symptoms for 2 hours.

An open-label extension study also demonstrated that the treatment arm had a similar adverse event profile as the care arm.[62] Ubrogepant was recently approved by the FDA for acute treatment of migraine with or without aura in adults.[63]

Rimegepant

The findings of the latest phase 3 trial that assessed the efficacy of rimegepant in the treatment of acute migraine against placebos were published in July 2019. The results were positive: 19.6% of patients were pain-free for 2 hours after taking rimegepant compared to 12.0% in placebos. Likewise, for freedom from most bothersome symptoms at 2 hours post-dose, it was 37.6% in rimegepant patients compared to 25.2% in placebos.[64]

Safety and tolerability were similar between treated patients and placebos, with nausea and urinary tract

Table 3. Migraine Drugs Approved in Last 5 Years

Drug Class and Name	Pharmaceutical Company	Brand Name	FDA Approval	Indication	Completed Phase 3 Trials
CGRP monoclonal antibodies					
Erenumab	Amgen/Novartis	Aimovig	17 May 2018	Preventive treatment of migraine in adults	ARISE[*] STRIVE[†] Liberty[‡]
Fremanezumab	Teva Pharmaceuticals	Ajovy	14 September 2018	Preventive treatment of migraine in adults	HALO I[§] HALO II[‖]
Galcanezumab	Eli Lily and Company	Emgality	27 September 2018	Preventive treatment of migraine in adults	EVOLVE 1[¶] EVOLVE 2[#] REGAIN[**]
Eptinezumab	Alder Biopharmaceuticals/ Lundbeck	Vyepti	21 February 2020	Preventive treatment of migraine in adults	PROMISE-1[††] PROMISE-2[‡‡]
5-HT_{1F} receptor agonists					
Lasmiditan	Eli Lilly and Company	Reyvow	11 October 2019	Acute treatment of migraine with or without aura in adults	SAMURAI[§§] SPARTAN[‖‖] GLADIATOR[¶¶]
CGRP receptor antagonists					
Ubrogepant	Allergan	Ubrelvy	23 December 2019	Acute treatment of migraine with or without aura in adults	ACHIEVE I[##] ACHIEVE II[***]

CGRP: Calcitonin Gene-Related Peptide; FDA: Food and Drug Administration

[*]Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, et al. ARISE: a phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia 2018;38:1026–37.

[†]Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, et al. A controlled trial of erenumab for episodic migraine. N Engl J Med 2017;377:2123–32.

[‡]Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. Lancet 2018;392:2280–7.

[§]Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. JAMA 2018;319:1999–2008.

[‖]Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med 2017;377:2113–22.

[¶]Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. JAMA Neurol 2018;75:1080–8.

[#]Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 phase 3 randomized controlled clinical trial. Cephalalgia 2018;38:1442–54.

[**]Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. Neurology 2018;91:e2211–21.

[††]Saper J, Lipton R, Kudrow D, Hirman J, Dodick D, Silberstein S, et al. Primary results of PROMISE-1 (Prevention Of Migraine via Intravenous eptinezumab Safety and Efficacy–1) trial: a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of eptinezumab for prevention of frequent episodic migraines. Neurology 2018;90:S20.001.

[‡‡]Lipton R. Eptinezumab for Prevention of Chronic Migraine: Results of 2 Quarterly Intravenous Infusions in the Phase 3 PROMISE-2 (Prevention Of Migraine via Intravenous eptinezumab Safety and Efficacy-2) Trial. Scientific Presentation at the American Headache Society Annual Meeting, 28 June–1 July 2018, San Francisco, CA, USA.

[§§]Kuca B, Silberstein SD, Wietecha L, Berg PH, Dozier G, Lipton RB. Lasmiditan is an effective acute treatment for migraine: a phase 3 randomized study. Neurology 2018;91:e2222–32.

[‖‖]Goadsby PJ, Wietecha LA, Dennehy EB, Kuca B, Case MG, Aurora SK, et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. Brain 2019;142:1894–904.

[¶¶]Eli Lilly and Company, CoLucid Pharmaceuticals. An open-label, long-term, safety study of lasmiditan for the acute treatment of migraine (GLADIATOR). Available at: https://clinicaltrials.gov/ct2/show/NCT02565186. Accessed on 22 March 2020.

[##]Dodick DW, Lipton RB, Ailani J, Lu K, Finnegan M, Trugman JM, et al. Ubrogepant for the treatment of migraine. N Engl J Med 2019;381:2230–41.

[***]Lipton RB, Dodick DW, Ailani J, Lu K, Finnegan M, Szegedi A, et al. Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: the ACHIEVE II randomized clinical trial. JAMA 2019;322:1887–98.

infections reported as the most common side effects. Specifically, issues with liver safety were not reported.[65] Currently, rimegepant is undergoing a phase 2 trial for migraine prevention. Should it prove successful, rimegepant will become the first gepant that is clinically proven to be effective in the treatment of acute migraine and prevention.

Atogepant

Atogepant is a novel, oral CGRP receptor antagonist that was designed to prevent migraine onset. It was described at the Scientific Meeting of the American Academy of Neurology and American Headache Society in 2018 and the results in patients with episodic migraine were reported to be promising. A total of 834 subjects were randomised across 5 different doses of atogepant and placebo. The findings included a mean reduction of 4 days in monthly migraine days in patients treated with atogepant.[66] At the time of writing, the findings have not been published. A phase 3 trial on prevention of chronic migraine is ongoing.[67]

Neuromodulation

Non-invasive neuromodulation represents a non-pharmacological modality of treatment. It modulates the pain experienced by migraine patients, but without any of the side effects associated with medication-taking in acute and preventive migraine therapy.

Single-Pulse Transcranial Magnetic Stimulation

Transcranial magnetic stimulation is widely used by neurologists for diagnostic and therapeutic purposes,[68] and is deemed safe and non-invasive. By leveraging on the concept of electromagnetic field, neurologists are able to deploy fluctuating magnetic waves to reach the cerebral cortex to induce weak electric currents that can modify the excitability of neurons.[69] Intially, this intervention was piloted in animal models to inhibit cortical spreading depression and modulate thalamocortical signalling.[70] With the development of single-pulse transcranial magnetic stimulation (sTMS), its use in migraine patients was evaluated in a sham controlled trial[71] and open-label trial[72] for acute therapy.

In the sham-controlled trial, a total of 164 patients were treated with sTMS. The study reported that the pain-free response rate at 2 hours was significantly better at 39% in the sTMS group compared to 22% in the sham group. Adverse events were comparable between sTMS and sham groups.[71]

In the open-label trial, ESPOUSE, the efficacy of sTMS in preventive migraine therapy was evaluated in 132 patients.[73] The findings of the study included a mean reduction of 2.75 headache days from a baseline of 9.06 days. Additionally, all pre-specified multiplicity-protected, secondary endpoints were met. The adverse events commonly reported in the study included light-headedness, tingling, tinnitus and dizziness. sTMS was approved by the FDA and the National Institute for Health and Care Excellence in the United Kingdom for acute and preventive treatment of migraine with and without aura.[74]

Conclusion

Over the last 3 decades, considerable progress was made to understand the pathophysiology of migraine. This led to a burgeoning tide of new treatment options that are mechanism-based and targeted. The recent introduction of pharmacological and non-pharmacological treatments described in this review offer millions of migraine patients from around the world hope of more effective and lasting relief from the condition.

REFERENCES

1. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1211–59.
2. Stewart WF, Wood C, Reed ML, Roy J, Lipton RB. Cumulative lifetime migraine incidence in women and men. Cephalalgia 2008;28:1170–8.
3. Loder E, Burch R, Rizzoli P. The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. Headache 2012;52:930–45.
4. Tfelt-Hansen P, Saxena PR, Dahlöf C, Pascual J, Láinez M, Henry P, et al. Ergotamine in the acute treatment of migraine: a review and European consensus. Brain 2000;123:9–18.
5. Goadsby PJ. The pharmacology of headache. Prog Neurobiol 2000;62:509–25.
6. Humphrey PP, Feniuk W, Perren MJ, Beresford IJ, Skingle M, Whalley ET. Serotonin and migraine. Ann N Y Acad Sci 1990;600:587–600.
7. Dodick D, Lipton RB, Martin V, Papademetriou V, Rosamond W, Van Den Brink AM, et al. Consensus statement: cardiovascular safety profile of triptans (5-HT1B/1D agonists) in the acute treatment of migraine. Headache 2004;44:414–25.
8. Lipton RB, Buse DC, Serrano D, Holland S, Reed ML. Examination of unmet treatment needs among persons with episodic migraine: results of the American Migraine Prevalence and Prevention (AMPP) Study. Headache 2013;53:1300–11.
9. Lipton RB, Munjal S, Buse DC, Alam A, Fanning KM, Reed ML, et al. Unmet acute treatment needs from the 2017 Migraine in America Symptoms and Treatment Study. Headache 2019;59:1310–23.
10. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB. Adherence to oral migraine—preventive medications among patients with chronic migraine. Cephalalgia 2015;35:478–88.

11. Lance JW. The pathophysiology of migraine. Ann Acad Med Singapore 1985;14:4–11.
12. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: a disorder of sensory processing. Physiol Rev 2017;97:553–622.
13. Hargreaves R, Olesen J. Calcitonin gene-related peptide modulators—the history and renaissance of a new migraine drug class. Headache 2019;59:951–70.
14. Ong JJY, Wei DYT, Goadsby PJ. Recent advances in pharmacotherapy for migraine prevention: from pathophysiology to new drugs. Drugs 2018;78:411–37.
15. Vila-Pueyo M. Targeted 5-HT_{1F} therapies for migraine. Neurotherapeutics 2018;15:291–303.
16. Mansfield C, Gebben DJ, Sutphin J, Tepper SJ, Schwedt TJ, Sapra S, et al. Patient preferences for preventive migraine treatments: a discrete-choice experiment. Headache 2019;59:715–26.
17. Aoki KR. Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. Neurotoxicology 2005;26:785–93.
18. United States Food and Drug Administration. Drug Approval Package: Aimovig (erenumab-aooe) injection. Statistical review(s). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761077Orig1s000TOC.cfm. Accessed on 22 March 2020.
19. United States Food and Drug Administration. Drug Approval Package: Ajovy (fremanezumab-vfrm). Available at: https://www accessdata.fda.gov/drugsatfda_docs/nda/2018/761089Orig1s000TOC.cfm. Accessed on 22 March 2020.
20. United States Food and Drug Administration. Drug Approval Package: Emgality (galcanezumab-gnlm). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761063Orig1s000TOC.cfm. Accessed on 22 March 2020.
21. Shi L, Lehto SG, Zhu DXD, Sun H, Zhang J, Smith BP, et al. Pharmacologic characterization of AMG334, a potent and selective human monoclonal antibody against the calcitonin gene-related peptide receptor. J Pharmacol Exp Ther 2016;356:223–31.
22. Sun H, Dodick DW, Silberstein S, Goadsby PJ, Reuter U, Ashina M, et al. Safety and efficacy of AMG334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol 2016;15:382–90.
23. Tepper S, Ashina M, Reuter U, Brandes JL, Doležil D, Silberstein S, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2017;16:425–34.
24. Ashina M, Dodick D, Goadsby PJ, Reuter U, Silberstein S, Zhang F, et al. Erenumab (AMG334) in episodic migraine: interim analysis of an ongoing open-label study. Neurology 2017;89:1237–43.
25. Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, et al. ARISE: a phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia 2018;38:1026–37.
26. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, et al. A controlled trial of erenumab for episodic migraine. N Engl J Med 2017;377:2123–32.
27. Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. Lancet 2018;392:2280–7.
28. Bigal ME, Escandon R, Bronson M, Walter S, Sudworth M, Huggins JP, et al. Safety and tolerability of LBR-101, a humanized monoclonal antibody that blocks the binding of CGRP to its receptor: results of the phase 1 program. Cephalalgia 2014;34:483–92.
29. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. JAMA 2018;319:1999–2008.
30. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med 2017;377:2113–22.
31. Benschop RJ, Collins EC, Darling RJ, Allan BW, Leung D, Conner EM, et al. Development of a novel antibody to calcitonin gene-related peptide for the treatment of osteoarthritis-related pain. Osteoarthritis Cartilage 2014;22:578–85.
32. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. JAMA Neurol 2018;75:1080–8.
33. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 phase 3 randomized controlled clinical trial. Cephalalgia 2018;38:1442–54.
34. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. Neurology 2018;91:e2211–21.
35. Tepper SJ. History and review of anti-calcitonin gene-related peptide (CGRP) therapies: from translational research to treatment. Headache 2018;58:S238–75.
36. H Lundbeck A/S. Corporate Release: FDA approves Lundbeck's VyeptiTM (eptinezumab-jjmr) – the first and only intravenous preventive treatment for migraine, 22 February 2020. Available at: https://investor.lundbeck.com/news-releases/news-release-details/fda-approves-lundbecks-vyeptitm-eptinezumab-jjmr-first-and-only. Accessed on 22 March 2020.
37. Dodick DW, Goadsby PJ, Silberstein SD, Lipton RB, Olesen J, Ashina M, et al. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial. Lancet Neurol 2014;13:1100–7.
38. Saper J, Lipton R, Kudrow D, Hirman J, Dodick D, Silberstein S, et al. Primary results of PROMISE-1 (Prevention Of Migraine via Intravenous eptinezumab Safety and Efficacy–1) trial: a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of eptinezumab for prevention of frequent episodic migraines. Neurology 2018;90:S20.001.
39. Lipton R. Eptinezumab for Prevention of Chronic Migraine: Results of 2 Quarterly Intravenous Infusions in the Phase 3 PROMISE-2 (Prevention Of Migraine via Intravenous eptinezumab Safety and Efficacy-2) Trial. Scientific Presentation at the American Headache Society Annual Meeting, 28 June–1 July 2018, San Francisco, CA, USA.
40. Loder E. Triptan therapy in migraine. N Engl J Med 2010;363:63–70.
41. Hall GC, Brown MM, Mo J, MacRae KD. Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. Neurology 2004;62:563–8.
42. United States Food and Drug Administration. News Release: FDA approves new treatment for patients with migraine, 11 October 2019. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-patients-migraine. Accessed on 22 March 2020.
43. Goadsby PJ, Classey JD. Evidence for serotonin (5-HT)1B, 5-HT1D and 5-HT1F receptor inhibitory effects on trigeminal neurons with craniovascular input. Neuroscience 2003;122:491–8.
44. Nelson DL, Phebus LA, Johnson KW, Wainscott DB, Cohen ML, Calligaro DO, et al. Preclinical pharmacological profile of the selective 5-HT1F receptor agonist lasmiditan. Cephalalgia 2010;30:1159–69.
45. Cohen ML, Schenck K. 5-Hydroxytryptamine(1F) receptors do not participate in vasoconstriction: lack of vasoconstriction to $LY_{344}86_4$,

a selective serotonin(1F) receptor agonist in rabbit saphenous vein. J Pharmacol Exp Ther 1999;290:935–9.

46. Krege JH, Rizzoli PB, Liffick E, Doty EG, Dowsett SA, Wang J, et al. Safety findings from phase 3 lasmiditan studies for acute treatment of migraine: results from SAMURAI and SPARTAN. Cephalalgia 2019;39: 957–66.
47. Kuca B, Silberstein SD, Wietecha L, Berg PH, Dozier G, Lipton RB. Lasmiditan is an effective acute treatment for migraine: a phase 3 randomized study. Neurology 2018;91:e2222–32.
48. Goadsby PJ, Wietecha LA, Dennehy EB, Kuca B, Case MG, Aurora SK, et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. Brain 2019;142:1894–904.
49. Brandes JL, Klise S, Krege JH, Case M, Khanna R, Vasudeva R, et al. Interim results of a prospective, randomized, open-label, phase 3 study of the long-term safety and efficacy of lasmiditan for acute treatment of migraine (the GLADIATOR study). Cephalalgia 2019;39:1343–57.
50. Eli Lilly and Company, CoLucid Pharmaceuticals. An open-label, long-term, safety study of lasmiditan for the acute treatment of migraine (GLADIATOR). Available at: https://clinicaltrials.gov/ct2/show/NCT02565186. Accessed on 22 March 2020.
51. Nappi G, Sandrini G, Sances G. Tolerability of the triptans: clinical implications. Drug Saf 2003;26:93–107.
52. Van Den Brink MA, Reekers M, Bax WA, Ferrari MD, Saxena PR. Coronary side-effect potential of current and prospective antimigraine drugs. Circulation 1998;98:25–30.
53. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurology 1990;28:183–7.
54. Goadsby PJ, Edvinsson L, Ekman R. Release of vasoactive peptides in the extracerebral circulation of humans and the cat during activation of the trigeminovascular system. Ann Neurology 1988;23:193–6.
55. Eftekhari S, Warfvinge K, Blixt FW, Edvinsson L. Differentiation of nerve fibers storing CGRP and CGRP receptors in the peripheral trigeminovascular system. J Pain 2013;14:1289–303.
56. Olesen J, Diener H, Husstedt IW, Goadsby PJ, Hall D, Meier U, et al. Calcitonin gene–related peptide receptor antagonist BIBN4096BS for the acute treatment of migraine. N Engl J Med 2004;350:1104–10.
57. Doods H, Hallermayer G, Wu D, Entzeroth M, Rudolf K, Engel W, et al. Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP antagonist. Br J Pharmacol 2000;129:420–3.
58. Ho TW, Connor KM, Zhang Y, Pearlman E, Koppenhaver J, Fan X, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. Neurology 2014;83:958–66.
59. Ho TW, Ho AP, Ge YJ, Assaid C, Gottwald R, MacGregor EA, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for prevention of headache in women with perimenstrual migraine. Cephalalgia 2016;36:148–61.
60. Dodick DW, Lipton RB, Ailani J, Lu K, Finnegan M, Trugman JM, et al. Ubrogepant for the treatment of migraine. N Engl J Med 2019;381:2230–41.
61. Lipton RB, Dodick DW, Ailani J, Lu K, Finnegan M, Szegedi A, et al. Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: the ACHIEVE II randomized clinical trial. JAMA 2019;322:1887–98.
62. Ailani J, Lipton RB, Hutchinson S, Knievel K, Lu K, Butler M, et al. Long-term safety evaluation of ubrogepant for the acute treatment of migraine: phase 3, randomized, 52-week extension trial. Headache 2020;60:141–52.
63. United States Food and Drug Administration. News Release: FDA approves new treatment for adults with migraine, 23 December 2019. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-adults-migraine. Accessed on 22 March 2020.
64. Lipton RB, Croop R, Stock EG, Stock DA, Morris BA, Frost M, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. N Engl J Med 2019;381:142–9.
65. Croop R, Goadsby PJ, Stock DA, Conway CM, Forshaw M, Stock EG, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. Lancet 2019;394:737–45.
66. Goadsby PJ, Dodick DW, Trugman JM, Finnegan M, Lakkis H , Lu K, et al. Orally administered atogepant was efficacious, safe, and tolerable for the prevention of migraine: results from a phase 2b/3 study. Neurology 2019;92:S17.001.
67. Allergan. Efficacy, safety, and tolerability of atogepant for the prevention of chronic migraine. Available at: https://clinicaltrials.gov/ct2/show/NCT03855137. Accessed on 22 March 2020.
68. Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol 2003;2:145–56.
69. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet 1985;1:1106–7.
70. Andreou AP, Holland PR, Akerman S, Summ O, Fredrick J, Goadsby PJ. Transcranial magnetic stimulation and potential cortical and trigeminothalamic mechanisms in migraine. Brain 2016;139:2002–14.
71. Lipton RB, Dodick DW, Silberstein SD, Saper JR, Aurora SK, Pearlman SH, et al. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. Lancet Neurol 2010;9:373–80.
72. Bhola R, Kinsella E, Giffin N, Lipscombe S, Ahmed F, Weatherall M, et al. Single-pulse transcranial magnetic stimulation (sTMS) for the acute treatment of migraine: evaluation of outcome data for the UK post market pilot program. J Headache Pain 2015;16:535.
73. Starling AJ, Tepper SJ, Marmura MJ, Shamim EA, Robbins MS, Hindiyeh N, et al. A multicenter, prospective, single arm, open label, observational study of sTMS for migraine prevention (ESPOUSE study). Cephalalgia 2018;38:1038–48.
74. eNeura, Inc. Press Release: eNeura, Inc. receives FDA clearance for acute treatment and prevention of migraine in children 12 years of age and older. Available at: http://www.eneura.com/press_releases/eneura-inc-receives-fda-clearance-for-acute-treatment-and-prevention-of-migraine-in-children-12-years-of-age-and-older/#. Accessed on 22 March 2020.

Review Article

The Link Between Amitriptyline and Movement Disorders: Clinical Profile and Outcome

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Abstract

Introduction: Amitriptyline (AMT) is a tricyclic antidepressant. In this review, we evaluate the clinical and epidemiological profile, pathological mechanisms and management of AMT-associated movement disorders. Materials and Methods: A search for relevant reports in 6 databases was performed. Studies that reported patients developed only ataxia or tremor after AMT use were excluded. Results: A total of 48 reports on 200 cases were found. AMT-associated movement disorders included myoclonus (n = 26), dyskinesia (n = 11), dystonia (n = 8), stutter (n = 5), akathisia (n = 3) and restless legs syndrome (n = 1). For less well-defined cases, 99 patients had dyskinesia, 19 had psychomotor disturbances, 3 had myoclonus, 11 had dystonia, 12 had Parkinsonism and 1 each had akathisia and extrapyramidal symptoms. Mean and standard deviation (SD) and median ages were 45.40 years (SD 16.78) and 40 years (range 3.7–82 years), respectively. Over half were women (58.13%) and the most common indication was depression. Mean and median AMT doses were 126 mg (SD 128.76) and 75 mg (range 15–800 mg), respectively. In 68% of patients, onset of movement disorders was <1 month; time from AMT withdrawal to complete recovery was <1 month in 70% of cases. A weak negative linear correlation (r = −0.0904) was found between onset of movement disorders and AMT dose. AMT withdrawal was the most common treatment. Conclusion: Amitriptyline is associated with various movement disorders, particularly myoclonus, dystonia and dyskinesias. Stutters and restless legs syndrome are some of the less common associations.

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Key words: Akathisia, Drug-induced, Dyskinesia, Dystonia, Myoclonus

Introduction

Amitriptyline (AMT) is classified as a tricyclic antidepressant (TCA). The development of AMT (Fig. 1) began in the mid-1950s after 2 American scientists, F Häfliger and Walter Schindler, serendipitously synthesised imipramine, the first TCA, when they replaced phenothiazine sulfur with ethylene in an attempt to develop a new antipsychotic drug.[1] The Swiss psychiatrist, Roland Kuhn, had studied imipramine in various psychiatric disorders, and he noted that depressive patients experienced good improvement in their quality of life after they were given imipramine.[2] His finding had since been confirmed by results from 60 studies.

Three years later, AMT was developed as a second TCA after the chemical structure of imipramine was modified with the substitution of C=CH with N-CH.[3] In April 1961, the United States (US) Food and Drug Administration (FDA) approved AMT (Elavil®, MK-230) for the treatment of depression.[4] In the following year, AMT was approved in the United Kingdom.[3] It is noteworthy that AMT is consistently ranked among the top 100 medications in the US after the FDA began to publish reports on the most frequently prescribed drugs in the country; it was ranked 54th in 1995, 40th in 2002 and 88th in 2016.[3,5]

To date, AMT is only approved for the treatment of depression. However, it has been used to treat other

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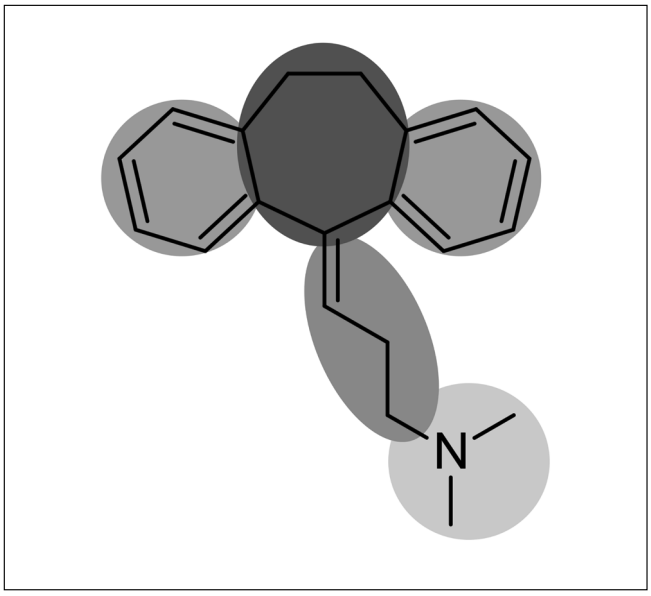

Fig. 1. Skeletal formula of the antidepressant drug amitriptyline, also known as 3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)-N, N-dimethylpropan-1-amine.

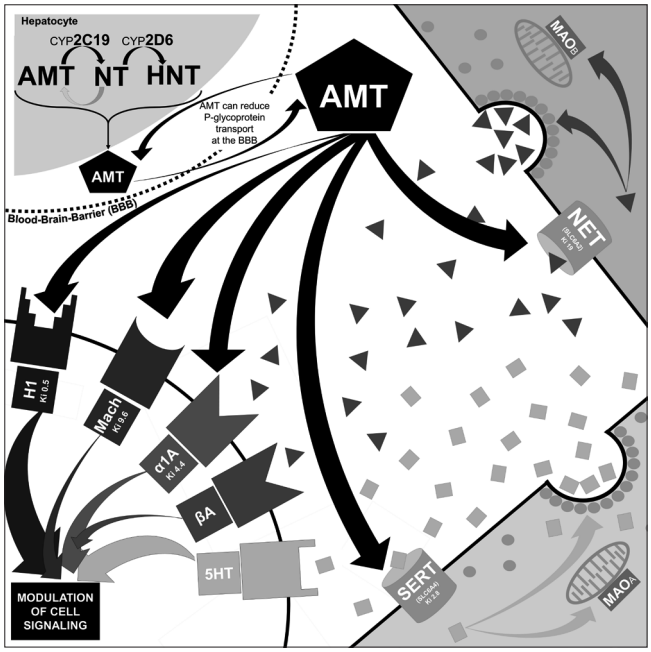

Fig. 2. Schematic diagram showing mechanism of action of AMT. After administration, AMT is metabolised in the liver to become HNT. AMT can reduce P-glycoprotein in BBB. AMT has 5 main actions: 1) block NET; 2) block SERT; 3) antagonism of alpha 1; 4) antagonism of H1; and 5) muscarinic acetylcholine receptors. The numerical values refer to the lower Ki found (the smaller the value, the stronger the drug binds to the site). Arrows pointing towards modulation of cell signalling are proportional to Ki. AMT: Amitriptyline; BBB: Blood-brain barrier; HNT: Hydroxynortriptyline; Ki: Inhibitory constant; NET: Norepinephrine transporter; NT: Nortriptyline; SERT: Serotonin transporter

conditions including anxiety, diabetic neuropathy, eating disorders, fibromyalgia, insomnia, irritable bowel syndrome, migraine prophylaxis, postherpetic neuralgia, post-traumatic stress disorder and sialorrhea.[6] After oral administration, AMT is easily absorbed into the gastrointestinal tract before it is metabolised in the liver by the cytochrome P450 2C19 (CYP2C19) to become nortriptyline (NT).[7] NT, in turn, is metabolised by CYP2D6 to become hydroxynortriptyline, which is the most abundant metabolite found in humans.[8] Athough a clear description of the metabolic pathway is lacking, studies of NT had found traces of AMT which strengthened the belief that AMT could be metabolised to become NT and vice versa.[9]

In 2017, Banks et al[10] reported that AMT caused a reduction in P-glycoprotein transport at the blood-brain barrier through the lysophosphatidic acid receptor 1. This finding proved significant since it paved the way for the development of new clinical strategies that could increase cerebral penetration of drugs that were associated with pharmacoresistance. The mechanism of action of AMT involves 5 principal routes: norepinephrine transporter block, serotonin transporter block, antagonism of alpha-1 (likely the main receptors related to the management of depression), antagonism of histamine H1 and muscarinic acetylcholine receptors (Fig. 2).[6–12]

The common adverse effects associated with AMT use are the result of alterations in the normal physiology of the receptors that are affected by the drug. They include acute angle glaucoma, blurred vision, confusion, dizziness, dry mouth, delirium, increased appetite, orthostatic hypotension, sedation, tachycardia, urinary retention and weight gain.[6,13] Some of the abnormal movements reported in clinical trials of AMT included lack of coordination, ataxia, tremors, restlessness and extrapyramidal symptoms such as tardive dyskinesias (DKN).[13]

In this review, we evaluate the clinical and epidemiological profile, pathological mechanisms and management of AMT-associated movement disorders.

Materials and Methods

The clinical characteristics and definitions of movement disorders such as akathisia (AKT), ballism, chorea, DKN, dystonia (DTN), myoclonus (MCL), Parkinsonism, restless legs syndrome (RLS), tic and tremor were based on the work of Jankovic and Tolosa.[14] Clinical diagnoses of psychiatric conditions were based on the diagnostic criteria published in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, by the American Psychiatric Association.[15] The Naranjo

algorithm was used to determine the likelihood of whether an adverse drug reaction could be attributed to the drug rather than the result of other factors.[16]

A search of 6 databases—Excerpta Medica, Google Scholar, Latin American and Caribbean Health Sciences Literature, MEDLINE, Scientific Electronic Library Online and ScienceDirect—was performed to identify case reports, case series, original articles, letters to the editor, bulletins and poster presentations published in electronic form between 1960–2019 on AMT-associated movement disorders. With the aid of Google Translate, the search was expanded to include publications in other languages including Chinese, Dutch, French, German, Italian, Japanese, Korean, Portuguese, Russian and Spanish. The search terms included ''akathisia'', ''ataxia'', ''ballism'', ''bradykinesia'', ''chorea'', ''dyskinesia'', ''dystonia'', ''hyperkinetic'', ''hypokinetic'', ''movement disorder'', ''myoclonus'', ''Parkinsonism'', ''restless legs syndrome'', ''restlessness'', ''stuttering'', ''tic'' and ''tremor''. The terms were also combined with ''Amitriptyline, MK-230''.

The authors independently screened the titles and abstracts of all papers that were identified from an initial search. Any disagreements were resolved through discussion between them.

The exclusion criteria included cases where the aetiology of movement disorders was already known and the motor symptoms had not worsened or were not related to AMT. Cases that could not be accessed by electronic means—including lack of response from authors to a formal request by electronic mail—were excluded. Reports of patients who only developed ataxia or tremor after AMT use were not included since details on the neurological examination and clarity in symptom description were lacking. Additionally, both disorders were mainly reported in clinical trials that used questionnaires to assess adverse effects and this could have led to a higher incidence in their reported diagnoses.[17] For cases that reported >1 factor that contributed to the development of movement disorders, the Naranjo algorithm was used to evaluate the probability of event occurrence.

Results of the search included details of author, department, year of publication, country of study, number of patients, AMT indication including off-label uses, time from first AMT dose to onset of movement disorder, time from AMT withdrawal to symptom improvement, patient's status at follow-up and significant findings of clinical history and management. The data were verified twice to ensure proper matching and were organised according to whether the movement disorder was a side effect of AMT use. Finally, categorical variables were presented as counts and continuous variables were shown as mean and standard deviation (SD), and as median and range.

Results

A total of 7516 reports were identified from the search, of which 6916 were excluded as they did not meet the inclusion and exclusion criteria (Fig. 3). Most reports did not indicate time of onset of movement disorders and recovery. Between 1960–2019, there were 48 reports of 200 patients—148 in North America, 41 in Europe and 11 in Asia—in 12 countries who developed AMT-associated movement disorders (Table 1).[18–65] Figure 4 depicts the trend in the number of AMT-associated movement disorders reported over the same period. AMT-associated movement disorders that were diagnosed in patients included MCL (n = 26), DKN (n = 11), DTN (n= 8), stuttering (n = 5), AKT (n = 3) and restless legs syndrome (n = 1). In less well-defined cases (Table 2), they included DKN (n = 99), psychomotor disturbances (n = 19), Parkinsonism (n = 12), DTN (n = 11), MCL (n = 3), AKT (n = 1) and extrapyramidal symptoms (n = 1).

For well-defined cases, 54 patients were identified and their mean and median ages were 45.40 years (SD 16.78) and 40 years (range 3.7–82 years), respectively. Over half of them were women (58.13%). Indications for AMT included depression (79.54%), insomnia, migraine, neuropathic pain and tension-type headache. Mean and median AMT dose were 126 mg (SD 128.76) and 75 mg (range 15–800 mg), respectively. AMT-associated movement disorders were diagnosed in patients after they were given the drug in the following doses: 15 mg (n = 2), 25 mg (n = 4), 32 mg (n = 1), 50 mg (n = 7), 60 mg (n = 1), 75 mg (n = 9), 100 mg (n = 4), 125 mg (n = 1), 150 mg (n = 11), 200 mg (n = 1), 300 mg (n = 5) and 800 mg (n = 1).

Time of onset of AMT-associated movement disorders was indicated in 44 patients. Mean and median time of onset was 40.95 days (SD 78.08) and 21 days, respectively; in 30 patients, it was <1 month. Duration from AMT withdrawal to complete recovery was described in 37 participants; it was <1 month in 26 patients and >1 month in remaining patients. A weak negative linear correlation ($r = -0.0904$) was found between start of AMT intake and onset of movement disorders ($P = 0.04$).

The treatment for AMT-associated movement disorders in 84.44% of patients was withdrawal of AMT. Other interventions included an increase or a reduction in AMT dose and the prescription of medications such as biperiden, diazepam, diphenhydramine, methylphenidate and phenobarbital. Reintroduction of AMT was attempted in 5 patients, but only 1 patient recovered without withdrawal.

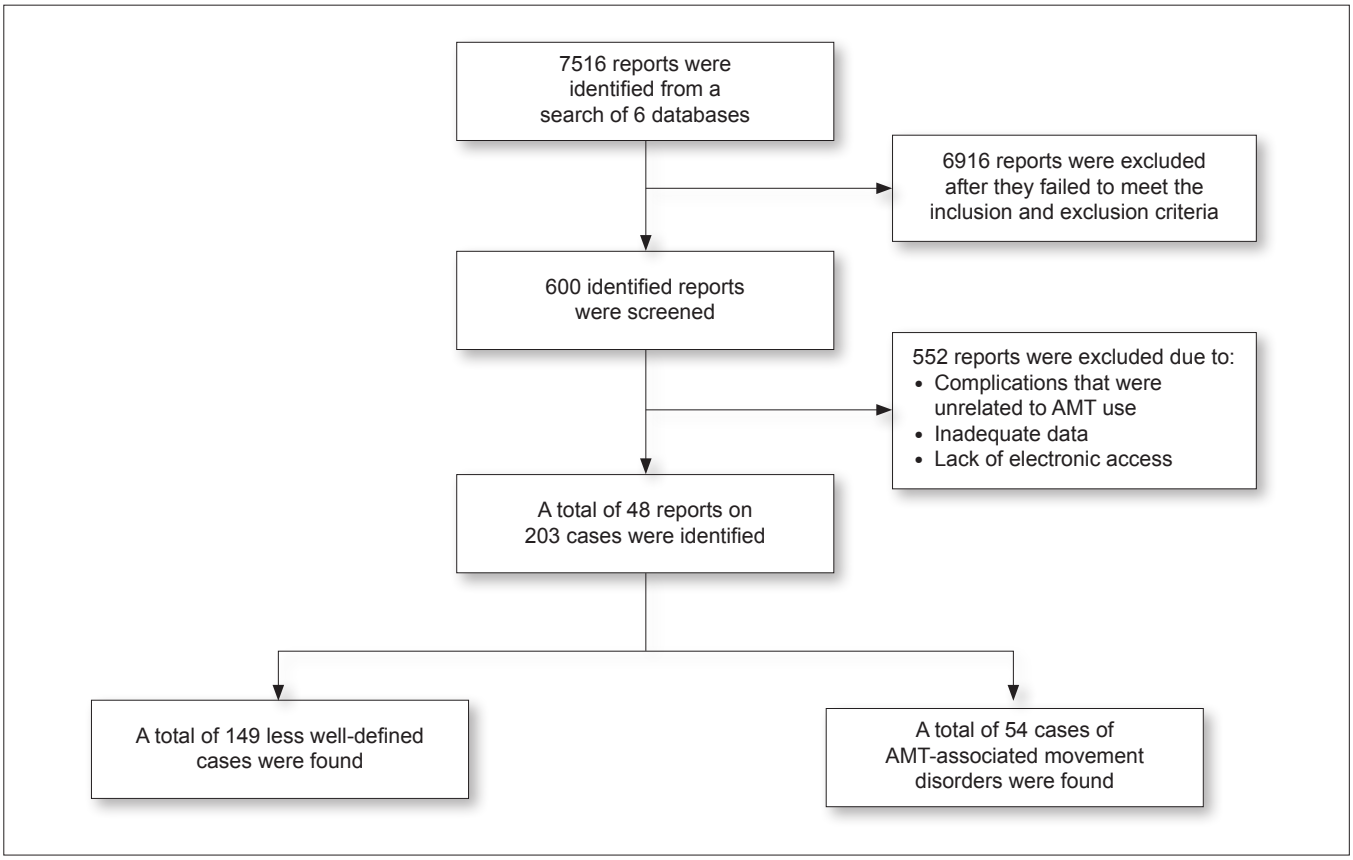

Fig. 3. Flow chart of search process. AMT: Amitriptyline

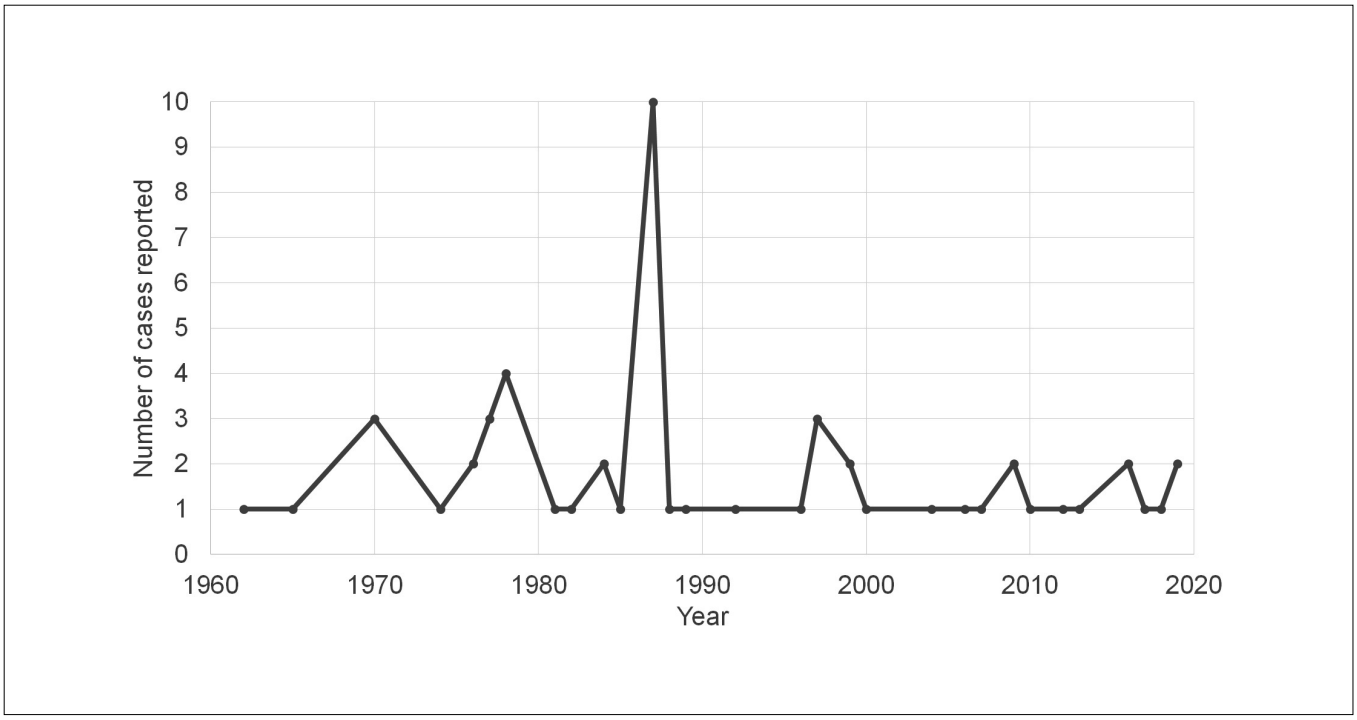

Fig. 4. Trend in clinical reports of amitriptyline-associated movement disorders between 1962–2019.

Table 1. Summary of Studies on AMT-Associated Movement Disorders

Study	Country, Year	Number of Cases	Age (Years)/ Gender	Indication	AMT Dose (mg)	AMT Start to MD Onset	AMT Withdrawal to Recovery	Outcome at Follow-Up	Clinical History and Management
Myoclonus									
Bockner[*]	UK, 1965	1	37/M	DPS	25	4 days	5 days	CR	CH: maybe cranial and multifocal MCL CM: AMT withdrawal and perphenazine started with improvement in MCL
Witton[†]	USA, 1965	1	44/M	DPS	75	7 days	2 days	CR	CH: focal MCL and DTN, normal EEG, possible interaction with thioridazine CM: Methylphenidate and phenobarbital started
Darcourt et al[‡]	France, 1970	3	61/F	DPS	NA	NA	NA	CR	CH: maybe cranial and multifocal MCL CM: no rechallenge
			64/F	DPS	NA	NA	NA	CR	CH: multifocal MCL CM: no rechallenge
			50/F	DPS	NA	NA	NA	CR	CH: multifocal MCL CM: no rechallenge
Burks et al[§]	USA, 1974	1	36/F	DPS	Overdose	NA	NA	CR	CH: multifocal MCL and choreiform DKN
Lippman et al[‖]	USA, 1977	1	25/F	DPS	150	3 days	1 day	CR	CH: multifocal MCL, apparent dose-related side effect CM: AMT withdrawal with symptom improvement; AMT rechallenge caused DKN; AMT withdrawal with recovery
Lippman et al[¶]	USA, 1977	1	58/F	DPS	125	5 days	1 day	CR	CH: multifocal MCL, apparent dose-related side effect CM: AMT withdrawal
Koller and Musa[#]	USA, 1985	1	14/NR	DPS	100	NR	NR	NR	CH: multifocal MCL

AKT: Akathisia; AMT: Amitriptyline; CH: Clinical history; CM: Clinical management; CR: Complete recovery; DKN: Dyskinesia; DPS: Depression; DTN: Dystonia; EEG: Electroencephalogram; EPS: Extrapyramidal symptoms; F: Female; HIV: Human immunodeficiency virus; M: Male; MCL: Myoclonus; MD: Movement disorder; NA: Not applicable/not available; NR: Not reported; PKN: Parkinsonism; UK: United Kingdom; USA: United States of America

[*]Bockner S. Side-effect of amitriptyline. Br Med J 1965;1:1188.

[†]Witton K. Severe toxic reaction to combined amitriptyline and thioridazine. Am J Psychiatry 1965;121:812–3.

[‡]Darcourt G, Fadeuilhe A, Lavagna J, Cazac A. Three cases of action myoclonus during treatment with imipramine and amitriptyline. Rev Neurol (Paris) 1970;122:141–2.

[§]Burks JS, Walker JE, Rumack BH, Ott JE. Tricyclic antidepressant poisoning: reversal of coma, choreoathetosis, and myoclonus by physostigmine. JAMA 1974;230:1405–7.

[‖]Lippmann S, Moskovitz R, O'Tuama L. Tricyclic-induced myoclonus. Am J Psychiatry 1977;134:90–1.

[¶]Lippmann S, Tucker D, Wagemaker H, Schulte T. A second report of tricyclic-induced myoclonus. Am J Psychiatry 1977;134:585–6.

[#]Koller WC, Musa MN. Amitriptyline-induced abnormal movements. Neurology 1985;35:1086.

Table 1. Summary of Studies on AMT-Associated Movement Disorders (Cont'd)

Study	Country, Year	Number of Cases	Age (Years)/ Gender	Indication	AMT Dose (mg)	AMT Start to MD Onset	AMT Withdrawal to Recovery	Outcome at Follow-Up	Clinical History and Management
Garvey and Tollefson[**]	USA, 1987	9	40 (mean)/ NR	DPS	150–300	2 weeks to 1 month	Weeks to months	CR	CH: Cranial MCL (n = 4), multifocal MCL (n = 3), nocturnal MCL (n =2) CM: AMT withdrawal
Foerstl et al[††]	Germany, 1989	1	62/F	DPS	150-300	1 year	1 week	CR	CH: multifocal myoclonus, Creutzfeldt-Jakob syndrome CM: AMT withdrawal
Nisijima et al[‡‡]	Japan, 1996	1	59/M	DPS	75	7 days	11 days	CR	CH: multifocal MCL, possible interaction with trazodone and lithium
Maher et al[§§]	Canada, 1997	1	40/M	DPS	25	NR	NR	Death	CH: multifocal MCL, possible differential diagnosis with HIV infection
Perry[‖‖]	UK, 1999	1	75/M	DPS	100	2 days	8 days	CR	CH: multifocal cortical MCL, EEG-based, previous episode of venlafaxine-induced MCL CM: AMT withdrawal
Choi et al[¶¶]	South Korea, 2006	1	64/M	Tension-type headache	15	8 days	1 day	CR	CH: multifocal MCL CM: AMT withdrawal and clonazepam started with symptom resolution
Kim and Yum[##]	South Korea, 2009	1	64/M	Tension-type headache	15	8 days	1 day	CR	CH: multifocal MCL CM: AMT withdrawal and clonazepam started with symptom resolution; AMT rechallenge with reappearance of MCL; AMT withdrawal with full recovery
Sreejayan and Praharaj[***]	India, 2013	1	30/M	Migraine	50	NR	8 days	CR	CH: cortical MCL, EEG-based, possible interaction with disulfiram CM: disulfiram withdrawal with recovery

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[**]Garvey MJ, Tollefson GD. Occurrence of myoclonus in patients treated with cyclic antidepressants. Arch Gen Psychiatry 1987;44:269–72.

[††]Foerstl J, Hohagen F, Hewer W, Pohlmann-Eden B. Another case of Creutzfeldt-Jakob like syndrome due to antidepressant toxicity. J Neurol Neurosurg Psychiatry 1989;52:920.

[‡‡]Nisijima K, Shimizu M, Abe T, Ishiguro T. A case of serotonin syndrome induced by concomitant treatment with low-dose trazodone and amitriptyline and lithium. Int Clin Psychopharmacol 1996;11:289–90.

[§§]Maher J, Choudhri S, Halliday W, Power C, Nath A. AIDS dementia complex with generalized myoclonus. Mov Disord 1997;12:593–7.

[‖‖]Perry NK. Venlafaxine-induced serotonin syndrome with relapse following amitriptyline. Postgrad Med J 2000;76:254–6.

[¶¶]Choi JP, Park SS, Park JS, Na SJ. A case of myoclonus presenting as a side effect of amitriptyline. J Korean Soc Clin Toxicol 2006;4:155–7.

[##]Kim YD, Yum KS. Tricyclic antidepressant-induced myoclonus: case report and literature review. Mov Disord 2009;24:70.

[***]Sreejayan K, Praharaj SK. Myoclonus associated with disulfiram. J Neuropsychiatry Clin Neurosci 2013;25:E37–9.

Table 1. Summary of Studies on AMT-Associated Movement Disorders (Cont'd)

Study	Country, Year	Number of Cases	Age (Years)/ Gender	Indication	AMT Dose (mg)	AMT Start to MD Onset	AMT Withdrawal to Recovery	Outcome at Follow-Up	Clinical History and Management
Paoletti et al[†††]	Italy, 2018	1	78/M	DPS	60	2 months	NR	CR	CH: multifocal subcortical MCL, normal EEG, stimulus sensitive, Creutzfeldt-Jakob syndrome CM: AMT withdrawal
Dyskinesia									
Fann et al[‡‡‡]	USA, 1976	2	37/M	DPS	150	6 weeks	2 weeks	CR	CH: orofacial DKN CM: AMT withdrawal with recovery; AMT rechallenge with reappearance of DKN; AMT withdrawal with recovery
			44/M	DPS	800	8 weeks	2 weeks	CR	CH: choreoathetoid DKN, apparent dose-related side effect CM: AMT withdrawal with symptom improvement; AMT rechallenge with reappearance of DKN; AMT withdrawal with recovery
Woogen et al[§§§]	USA, 1981	1	57/F	DPS	75	4 days	NR	No	CH: orofacial DKN and limb choreiform DKN CM: AMT withdrawal
Gangat et al[‖‖‖]	Ireland, 1987	1	69/F	DPS	75	3 weeks	3 days	CR	CH: orofacial DKN CM: AMT withdrawal; trimipramine started with reappearance of DKN; drug was withdrawn
Gourzis et al[¶¶¶]	Greece, 2004	1	65/F	DPS	50	1 month	1 week	CR	CH: orofacial DKN (rabbit syndrome), possible interaction with paroxetine and perphenazine CM: paroxetine discontinued with symptom resolution.

AKT: Akathisia; AMT: Amitriptyline; CH: Clinical history; CM: Clinical management; CR: Complete recovery; DKN: Dyskinesia; DPS: Depression; DTN: Dystonia; EEG: Electroencephalogram; EPS: Extrapyramidal symptoms; F: Female; HIV: Human immunodeficiency virus; M: Male; MCL: Myoclonus; MD: Movement disorder; NA: Not applicable/not available; NR: Not reported; PKN: Parkinsonism; UK: United Kingdom; USA: United States of America

[†††] Paoletti FP, Di Gregorio M, Calabresi P, Parnetti L. Drug-induced Creutzfeldt-Jakob disease-like syndrome: early CSF analysis as useful tool for differential diagnosis. BMJ Case Rep 2018;11:e224314.

[‡‡‡]Fann WE, Sullivan JL, Richman BW. Dyskinesias associated with tricyclic antidepressants. Br J Psychiatry 1976;128:490–3.

[§§§]Woogen S, Graham J, Angrist B. A tardive dyskinesia-like syndrome after amitriptyline treatment. J Clin Psychopharmacol 1981;1:34–6.

[‖‖‖]Gangat AE, Luiz HA, Kajee AH, Ibrahim NI, Simpson MA. Tricyclic-induced acute tardive dyskinesia. A case report. S Afr Med J 1987;71:729.

[¶¶¶]Gourzis P, Polychronopoulos P, Argyriou AA, Bakalidou C, Beratis S. Induction of the rabbit syndrome following coadministration of paroxetine, perphenazine, and amitriptyline. Clin Neuropharmacol 2004;27:299–300.

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Simpson and Whitfield[###]	UK, 2007	1	39/M	NR	NR	NR	1 day	CR	CH: choreiform DKN, positive deficiency of CYP2D6 CM: AMT withdrawal
Callista and Emidio[****]	Italy, 2014	1	29/F	Migraine	32	<1 month	1 month	CR	CH: orofacial DKN (rabbit syndrome) CM: AMT withdrawal; diazepam and biperiden started with symptom resolution
Pawar and Woo[††††]	USA, 2010	1	82/F	Insomnia	50	1 year	2 days	CR	CH: orofacial DKN, possible interaction with amiodarone CM: AMT withdrawal; benztropine and diphenhydramine started
Philips and Augustine[‡‡‡‡]	India, 2017	1	58/F	DPS	75	2 months	10 days	CR	CH: choreoathetoid DKN, history of Parkinson's disease CM: AMT withdrawal; baclofen and amantadine started with improvement in DKN
Kumar et al[§§§§]	India, 2019	1	25/F	NR	25	NR	1 day	CR	CH: orofacial and limb DKN, possible interaction with estrogen and progesterone CM: AMT withdrawal and benzodiazepine started with symptom resolution
Mithun[‖‖‖‖]	India, 2019	1	38/F	Insomnia	25	15 days	6 days	CR	CH: limb DKN CM: AMT withdrawal and clonazepam started with symptom resolution
Stuttering									
Quader[¶¶¶]	UK, 1977	1	48/F	DPS	150	4 days	NR	CR	CH: maybe stuttering, rapid with increase in AMT dose CM: AMT withdrawal

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[###]Simpson SM, Whitfield A. An unusual cause of movement disorder in a young man with penile carcinoma. J Pain Symptom Manage 2007;33:656–8.

[****]Callista G, Di Emidio G. A case of "rabbit syndrome" induced by amitriptyline. Eur Neuropsychopharmacol 2014;24:S740.

[††††]Pawar PS, Woo DA. Extrapyramidal symptoms with concomitant use of amitriptyline and amiodarone in an elderly patient. Am J Geriatr Pharmacother 2010;8:595–8.

[‡‡‡‡]Philips CA, Augustine P. Amitriptyline induced tardive dyskinesia in a patient with cirrhotic Parkinsonism. India J Med Specialities 2017;8:86–8.

[§§§§]Kumar M, Vijayavarman V, Singh AK. Acute extrapyramidal symptoms associated with concomitant use of amitriptyline and oral contraceptive pills: a case report. J Med Sci Clin Res 2019;7:1024–6.

[‖‖‖‖]Mithun S. Amitriptyline induced acute dyskinesia. Int J Health Sci Pharmacy 2019;3:40–2.

[¶¶¶]Quader SE. Dysarthria: an unusual side effect of tricyclic antidepressants. Br Med J 1977;2:97.

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Study	Country, Year	Number of Cases	Age (Years)/ Gender	Indication	AMT Dose (mg)	AMT Start to MD Onset	AMT Withdrawal to Recovery	Outcome at Follow-Up	Clinical History and Management
Schatzberg et al[####]	USA, 1978	3	49/F	DPS	200	19 days	NR	NR	CH: maybe stuttering (speech blockage) CM: AMT withdrawal
			40/F	DPS	150	28 days	NR	NR	CH: maybe stuttering (speech blockage) CM: diazepam or increase in AMT dose without improvement in symptoms
			56/M	DPS	150	18 days	NR	NR	CH: maybe stuttering (speech blockage) CM: AMT withdrawal
Sholomskas[*****]	USA, 1978	1	25/M	DPS	100	7 days	2 days	CR	CH: maybe stuttering (speech blockage), apparent dose-related side effect CM: AMT withdrawal
Dystonia									
Finder et al[†††††]	USA, 1982	1	30/M	DPS	75	1 day	NA	CR	CH: cervical DTN (retrocollis) CM: diphenhydramine started with symptom resolution; AMT rechallenge caused symptoms; benztropine started with symptom resolution; AMT rechallenge with no new symptoms
Lee[‡‡‡‡‡]	USA, 1988	1	30/F	Insomnia	75	1 day	1 day	CR	CH: segmental upper limb DTN CM: AMT withdrawal
Ornadel et al[§§§§§]	UK, 1992	1	20/M	DPS	50	3 months	NR	CR	CH: segmental lower limb with axial and oromandibular DTN CM: AMT withdrawal and procyclidine started with symptom resolution
Suzuki et al[‖‖‖‖‖]	Japan, 1997	1	58/M	DPS	150	19 days	4 days	CR	CH: axial DTN CM: biperiden started with symptom resolution

AKT: Akathisia; AMT: Amitriptyline; CH: Clinical history; CM: Clinical management; CR: Complete recovery; DKN: Dyskinesia; DPS: Depression; DTN: Dystonia; EEG: Electroencephalogram; EPS: Extrapyramidal symptoms; F: Female; HIV: Human immunodeficiency virus; M: Male; MCL: Myoclonus; MD: Movement disorder; NA: Not applicable/not available; NR: Not reported; PKN: Parkinsonism; UK: United Kingdom; USA: United States of America

[####]Schatzberg AF, Cole JO, Blumer DP. Speech blockage: a tricyclic side effect. Am J Psychiatry 1978;135:600–1.

[*****]Sholomskas AJ. Speech blockage in young patients taking tricyclics. Am J Psychiatry 1978;135:1572–3.

[†††††]Finder E, Lin KM, Ananth J. Dystonic reaction to amitriptyline. Am J Psychiatry 1982;139:1220.

[‡‡‡‡‡]Lee HK. Dystonic reactions to amitriptyline and doxepin. Am J Psychiatry 1988;145:649.

[§§§§§]Ornadel D, Barnes EA, Dick DJ. Acute dystonia due to amitriptyline. J Neurol Neurosurg Psychiatry 1992;55:414.

[‖‖‖‖‖]Suzuki T, Kurita H, Hori T, Sasaki M, Baba A, Shiraishi H, et al. The Pisa syndrome (pleurothotonus) during antidepressant therapy. Biol Psychiatry 1997;41:234–6.

Table 1. Summary of Studies on AMT-Associated Movement Disorders (Cont'd)

Study	Country, Year	Number of Cases	Age (Years)/ Gender	Indication	AMT Dose (mg)	AMT Start to MD Onset	AMT Withdrawal to Recovery	Outcome at Follow-up	Clinical History and Management
Le Doze et al¶¶¶¶	France, 1999	1	72/F	Neuropathy	75	>6 weeks	NA	CR	CH: blepharospasm and oromandibular DTN, possible interaction with ranitidine CM: Lowered AMT dose and ranitidine withdrawal with symptom resolution
Cappuccio et al####	Italy, 2013	1	3.7/F	Neuropathic pain	0.4 mg/kg daily	5 days	NR	CR	CH: apparently segmental inferior limb with cervical (retrocollis) and axial DTN, history of metachromatic leukodystrophy CM: AMT withdrawal
Gedam et al****	India, 2017	1	32/F	DPS	50	2.5 months	1 day	CR	CH: oromandibular dystonia, possible interaction with paroxetine CM: AMT withdrawal and promethazine started with symptom resolution
Hiremath and Desai††††††	India, 2016	1	28/M	DPS	50–75	6 months	1 day	CR	CH: cervical DTN CM: AMT withdrawal and promethazine started with DTN recovery
Restless legs syndrome									
Krishnan et al‡‡‡‡‡	USA, 1984	1	35/F	DPS	50	Single dose	2 days	CR	CH: possible interaction with estrogen and progesterone CM: AMT withdrawal
Akathisia									
Krishnan et al‡‡‡‡‡	USA, 1984	1	51/F	DPS	50	Single dose	NR	CR	CM: AMT withdrawal
Vandel et al§§§§§§	France, 1997	1	70/F	DPS	100	1 month	NA	CR	CM: Reduction in AMT dose
Yotsui et al‖‖‖‖‖‖	Japan, 2000	1	NR	DPS	NR	NA	NA	NA	CH: likely AMT-induced, AKT developed after epidural droperidol use but was already on AMT and amlodipine

AKT: Akathisia; AMT: Amitriptyline; CH: Clinical history; CM: Clinical management; CR: Complete recovery; DKN: Dyskinesia; DPS: Depression; DTN: Dystonia; EEG: Electroencephalogram; EPS: Extrapyramidal symptoms; F: Female; HIV: Human immunodeficiency virus; M: Male; MCL: Myoclonus; MD: Movement disorder; NA: Not applicable/not available; NR: Not reported; PKN: Parkinsonism; UK: United Kingdom; USA: United States of America

¶¶¶¶Le Doze F, Moulin M, Defer GL. Meige's syndrome in a patient treated with ranitidine. Mov Disord 1999;14:175–7.

####Cappuccio G, Brunetti-Pierri N, Terrone G, Romano A, Andria G, Del Giudice E. Low-dose amitriptyline-induced acute dystonia in a patient with metachromatic leukodystrophy. JIMD Rep 2013;9:113–6.

****Gedam SR, Goyal A, Shivji IA. Acute dystonia with concomitant use of amitriptyline and paroxetine. Open J Psychiatry Allied Sci 2017;8:84–6.

††††††Hiremath SB, Desai M. Amitriptyline induced cervical dystonia. J Sci Soc 2016;43:38–40.

‡‡‡‡‡Krishnan KR, France RD, Ellinwood Jr EH. Tricyclic-induced akathisia in patients taking conjugated estrogens. Am J Psychiatry 1984;141:696–7.

§§§§§§Vandel P, Bonin B, Leveque E, Sechter D, Bizouard P. Tricyclic antidepressant-induced extrapyramidal side effects. Eur Neuropsychopharmacol 1997;7:207–12.

‖‖‖‖‖‖Yotsui H, Matsunaga M, Katori K, Kohno S, Higa K. Extrapyramidal reactions after epidural droperidol. Masui 2000;49:1152–4.

Table 2. Summary of Studies on Less Well-Defined Cases of AMT-Associated Movement Disorders

Study	Country	Year	Number of Cases	Indication	Clinical History and Management
National Drugs Advisory Board*	Ireland	1975	1	Dystonia	Report on side effects of AMT use between 1968–74.
National Drugs Advisory Board†	Ireland	1977	1	Dystonia	Report on side effects of AMT use in 1976. The single case was likely a result of the interaction between AMT and perphenazine.
Schimdt et al‡	Germany	1984	19	Psychomotor disturbances	Report on adverse reactions of psychotropic drugs in a psychiatry university hospital; 19 patients reported a psychomotor disturbance after AMT use.
Miller and Jankovic§	USA	1990	35	Movement disorder	Of 125 patients referred for drug-induced movement disorders, 38 had used AMT and perphenazine; 14 had dyskinesia, 9 had dystonia, 11 had Parkinsonism and 1 had akathisia.
Spigset et al‖	Sweden	1997	3	Myoclonus	Myoclonus was reported after treatment with antidepressants in 3 patients who were given daily dose of AMT 50 mg, 75 mg and 100 mg. Some patients had the CYP2D6 inhibitor that could have predisposed them to develop myoclonus.
Madhusoodanan et al¶	USA	2010	1	Extrapyramidal symptoms	A single case of AMT-associated extrapyramidal symptom was lodged with the FDA Adverse Event Reporting System.
Bondon-Guitton et al#	France	2011	1	Parkinsonism	Review of spontaneous notifications of drug-associated Parkinsonism between 1993–2009.
Hunter et al**	USA	2019	85	Dyskinesia	Of 434 patients referred for drug-induced movement disorders, 85 had used AMT and perphenazine.

AMT: Amitriptyline; FDA: Food and Drug Administration; USA: United States of America

*National Drugs Advisory Board, Ireland. Reports of Side Effects Associated with the Use of Drugs 1968–1975. Dublin: Charles Lucas House; 1976.

†National Drugs Advisory Board, Ireland. Reports of Side Effects Associated with the Use of Drugs 1976. Dublin: Charles Lucas House; 1977.

‡Schmidt LG, Grohmann R, Helmchen H, Langscheid-Schmidt K, Müller-Oerlinghausen B, Poser W, et al. Adverse drug reactions. An epidemiological study at psychiatric hospitals. Acta Psychiatr Scand 1984;70:77–89.

§Miller LG, Jankovic J. Neurologic approach to drug-induced movement disorders: a study of 125 patients. South Med J 1990;83:525–32.

‖Spigset O, Hedenmalm K, Dahl ML, Wiholm BE, Dahlqvist R. Seizures and myoclonus associated with antidepressant treatment: assessment of potential risk factors, including CYP2D6 and CYP2C19 polymorphisms, and treatment with CYP2D6 inhibitors. Acta Psychiatr Scand 1997;96:379–84.

¶Madhusoodanan S, Alexeenko L, Sanders R, Brenner R. Extrapyramidal symptoms associated with antidepressants—a review of the literature and an analysis of spontaneous reports. Ann Clin Psychiatry 2010;22:148–56.

#Bondon-Guitton E, Perez-Lloret S, Bagheri H, Brefel C, Rascol O, Montastruc J-L. Drug-induced Parkinsonism: a review of 17 years' experience in a regional pharmacovigilance center in France. Mov Disord 2011;26:2226–31.

**Hunter CB, Kenney C, Mejia N, Davidson A, Jankovic J. Medications Associated with the Onset of Tardive Dyskinesia. Available at: https://www.bcm.edu/neurology/pdf/poster_pdcmdc_Meds_TDysk_ANA.pdf. Accessed on 31 January 2020.

After treatment, 47 (95.91%) patients recovered fully, 1 succumbed to human immunodeficiency virus-related complications and 1 experienced a partial recovery.

Discussion

The findings of this review can be summarised with the aid of a hypothetical case based on the information shown in Table 1. After a middle-aged woman of North American origin presented to her psychiatrist with depressive symptoms, she was prescribed AMT 25 mg and the dose was gradually increased to between 100–150 mg. Within 1 month, she returned to the clinic with complaint of involuntary jerks that involved mainly her upper limbs. Results of her laboratory tests were normal and electrodiagnostic studies were not performed. AMT was discontinued without any symptomatic treatment. At follow-up 1 month later, she made a full recovery.

In light of the findings of this review, some of the AMT-associated movement disorders are discussed in the following sections. The pathophysiological mechanisms that are hypothesised to be responsible for the development of movement disorders after the use of AMT are shown in Figure 5.

Myoclonus

MCL was the first movement disorder to be reported after AMT was approved for use in patients by the FDA. MCL patients tended to be men who were prescribed a lower dose of AMT. MCL onset and recovery times were reported to take place within days. Most studies did not report the results of electrodiagnostic examinations in this

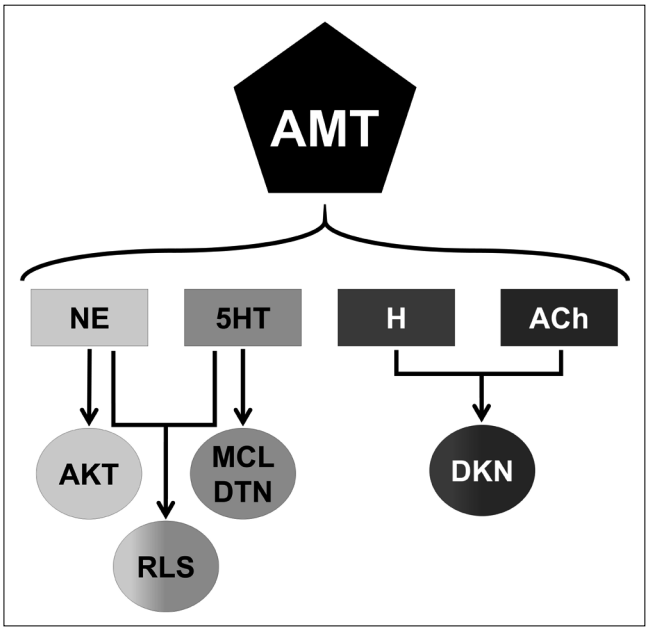

Fig. 5. Schematic diagram of pathophysiological mechanisms proposed in the development of AMT-associated movement disorders. 5HT: Serotonin; ACh: Acetylcholine; AKT: Akathisia; AMT: Amitriptyline; DKN: Dyskinesia; DTN: Dystonia; H: Histamine; MCL: Myoclonus; NE: Norepinephrine; RLS: Restless legs syndrome

group of patients; in those that did, an abnormal/normal electroencephalogram was reported.[58,62] Consequently, AMT-induced MCL may have a cortical and subcortical source.[66] MCL can be classified into multifocal, palatal and cranial types. Based on the clinical features suggested by Gupta and Lang,[67] it is possible that cranial MCL is associated with bupropion.

It is likely that MCL onset is dose-dependent. A reduction in frequency of bodily jerks was reported after the dose of AMT was lowered in 2 studies,[25,26] but this result was not replicated in other studies. Additionally, 2 studies reported onset of Creutzfeldt-Jakob syndrome—characterised by rapid cognitive deterioration, MCL and Parkinsonian features—that resolved after AMT was withdrawn.[38,62] The most common treatment for MCL was withdrawal of AMT. It is also possible that a short trial of benzodiazepine may reduce the symptoms and accelerate recovery.[68]

Like other antidepressants, AMT is thought to trigger off increased serotonin activity that leads to MCL onset.[69] The study by Lhermitte et al[70] was the first to suggest a link between serotonin and the development of MCL. Subsequently, studies have associated the development of MCL with an increase or decrease in serotonin concentration.[71] In particular, findings from animal studies that involved the use of guinea pigs had found that the interaction between 2 serotonin receptors, 5-HT1A and 5-HT2, could induce MCL.[69,72]

Dyskinesia

In DKN, patients present with dyskinetic orofacial, limb or choreoathetoid movements. In 1 patient, DKN reappeared after AMT was withdrawn due to its onset and after trimipramine was prescribed.[35] Consequently, it is possible that DKN can have a class effect and it is probably prudent to abstain from further treatment with other TCA.[35]

In 2 patients, rabbit syndrome was seen. In this condition, perioral tremors occur at a rate of 4–5 Hz and are attributed to the extrapyramidal effects of antipsychotic drugs.[49,52] Although it is included as an adverse effect in the discussion of DKN in this review, some authors have contended that it should be treated as a different type of disorder.

DKN onset has been attributed to abnormal adaptation of the striatal network that leads to overactivation of the direct pathway.[73] This could be supported by its long onset time in patients that lasted from weeks to months which was longer than the average time of onset.

The interference of AMT with histamine receptors could have also led to the development of DKN. These receptors are commonly found throughout the central nervous system. However, the largest concentration of these receptors are found in the tuberomammillary nucleus which is connected to the cerebral cortex, neostriatum, hypothalamus, hippocampus and nucleus accumbens.[74] Consequently, in susceptible individuals, AMT could have an effect on receptor H1 that led to the release of oxidative species and resulted in striatal disorganisation.[73]

Another possible explanation for DKN onset is a decrease in cholinergic activity induced by AMT use that led to an imbalance in dopamine. In fact, findings from brain autopsy of patients with Huntington's disease had shown an increase in the ratio of dopamine to acetylcholine.[75]

Dystonia

DTN patients tended to be younger and were prescribed a lower dose of AMT. In descending order of frequency, the symptoms of DTN included oromandibular, axial, segmental limb, cervical and blepharospasm movements. In patients with metachromatic leukodystrophy, AMT use at doses that are lower than the maintenance dose can lead to DTN onset.[57] Treatment of DTN involved withdrawal of AMT and complete recovery was achieved within days, even though most reports did not indicate the duration.

In some studies, patients who were on AMT for a longer duration developed DTN after the dose was increased.[60]

Consequently, it is hypothesised that AMT-induced DTN is more likely to be a threshold effect rather than an adverse, linear dose-dependent effect.

It is difficult to attribute the development of DTN to an anticholinergic mechanism since it is well known that anticholinergic medications such as trihexyphenidyl can, in fact, alleviate it.[76] Instead, most researchers believed that DTN develops as a result of an imbalance in dopamine and acetylcholine.[77,78] Consequently, involvement of a serotoninergic pathway in the striatum may provide a reasonable explanation (Fig. 6).[79–81] Findings from animal models had shown that the use of selective serotonin inhibitors could increase serotonin concentrations and lead to inactivation of dorsal raphe nucleus.[82] Since dorsal raphe nucleus is believed to control both direct and indirect pathways,[80,83] its absence or malfunction will likely lead to a rise in dopamine that, in turn, activate in excess the direct pathway that facilitates movement and, eventually, causes DTN.[79,81]

Stuttering

The word ''stuttering'' was not used in any of the studies; instead, the term ''speech blockage'' was used.[28] Since there was a lack of clarity in the clinical description and management of patients in the studies, it was possible that they could have presented with oromandibular DTN or palatal MCL which were associated with stuttering.[84]

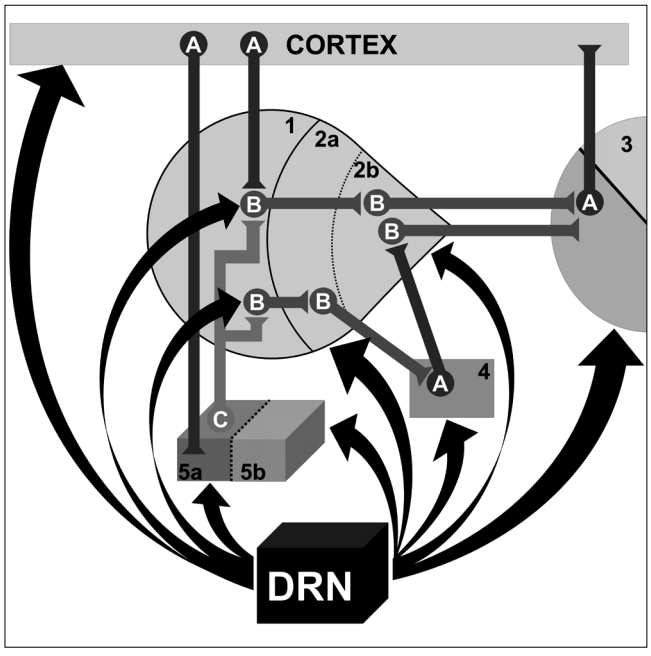

Fig. 6. Schematic diagram showing serotoninergic modulation of basal ganglia circuits. The dorsal raphe nucleus (DRN) provides serotonergic inputs to all components of basal ganglia; these pathways are identified by tryptophan hydroxylase immunoreactivity. 1: Caudate and putamen; 2a: External globus pallidus (GP); 2b: Internal GP; 3: Thalamus; 4: Subthalamus; 5a: Substantia nigra (SN) pars compacta; 5b: SN pars reticulata; A: Glutamatergic neurotransmission; B: Gabaergic; C: Dopaminergic

As all the cases were reported within a short span of 2 years, this finding could be attributed to problems in the formulation of AMT during this period rather than a common pathophysiological mechanism related to the interactions between receptors.

In the patients, AMT dose ranged from moderate to high (100–200 mg). In 1 patient, the stuttering did not improve even after the dose was increased. In another patient, a dose-dependent effect was observed after a reduction in the dose led to a decrease in speech blockage.[28,29]

Akathisia

In clinical practice, it is common knowledge that an association exists between AKT and AMT. However, it was not found in this review and only 3 studies had cited AKT as a possible diagnosis. This movement disorder was even observed in patients who were given a lower dose of AMT.[48] It was treated with either withdrawal of AMT or a reduction in AMT dose that led to resolution of symptoms.

It is likely that AMT-induced AKT is linked to an increase in noradrenergic activity. Findings from studies of rat models had shown that noradrenaline injections promoted the release of dopamine—mainly in the orbitofrontal cortex—and led to hyperactivation of the dopamine receptor D1 which induces restlessness that resembles AKT symptoms in humans.[85,86]

Restless Legs Syndrome

In 1 patient, RLS could be attributed to the interaction between AMT and an oral contraceptive that produced estrogens and progestins which weakened the effect of TCA and increased TCA plasma concentration.[7] A similar finding by Kumar et al[64] led them to suggest it as a possible cause of DKN. Some of the adverse effects associated with AMT use were related to lowered metabolism of cytochrome P450 2D6 (CYP2D6).[87] It is believed that when an increase in the concentration of AMT and NT—not hydroxynortriptyline—takes place, there is a greater likelihood of side effects developing. This was observed in patients with lower metabolic rate or who were on medications that inhibit CYP2D6.

There was only 1 patient who developed RLS after AMT use. However, since this condition is commonly reported in patients who were on other TCA, the finding of RLS in this patient was treated as a class effect.[88] In their study of the association between antidepressant use, gender and RLS in >1500 patients, Baughman et al

found that AMT-associated RLS was more common in men (relative risk 2.40, confidence interval 1.45–4.00).[89]

The aetiology of AMT-associated RLS is attributed to an increase in serotoninergic activity. It is theorised that inhibition of the serotonin transporter leads to a rise in serotonin concentration that has an effect on the intermediolateral nucleus.[90] This effect causes the postganglionic adrenal glands to release norepinephrine that result in vascular alterations and provoke a sensation of discomfort in the inferior limbs.[91]

Conclusion

AMT is associated with various movement disorders, particularly DKN, DTN and MCL. Stutters and RLS are some of the less common associations. The pathophysiological mechanism of AMT-induced AKT is likely related to norepinephrine; in RLS, it is attributed to norepinephrine and serotonin; in DTN and MCL, it is ascribed to serotonin; and in DKN, histamine and acetylcholine. AMT is the most commonly prescribed TCA, which explains the large number of adverse effects reported from its use in the literature. A correlation between AMT dose and onset of movement disorders has been suggested. Findings on AMT-induced movement disorders can enrich the understanding of the effects of other TCA. More studies are needed to understand the pathophysiology of AMT and other TCA in movement disorders.

REFERENCES

1. Schindler W, Häfliger F. Derivatives of iminodibenzyl. Helv Chim Acta 1954;37:472–83.
2. Kuhn R. The imipramine story. In: Ayd F, Blackwell B, editors. Discoveries in Biological Psychiatry. Philadelphia: Lippincott; 1970.
3. Fangmann P, Assion H-J, Juckel G, González CA, López–Muñoz F. Half a century of antidepressant drugs: on the clinical introduction of monoamine oxidase inhibitors, tricyclics, and tetracyclics. Part II: tricyclics and tetracyclics. J Clin Psychopharmacol 2008;28:1–4.
4. Barsa JA, Sauders JC. Amitriptyline (Elavil), a new antidepressant. Am J Psychiatry 1961;117:739–40.
5. ClinCalc DrugStats Database. The Top 300 Drugs of 2020. Available at: https://clincalc.com/DrugStats/. Accessed on 31 January 2020.
6. Thour A, Marwaha R. Amitriptyline. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2020.
7. Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017;102:37–44.
8. Rudorfer MV, Potter WZ. Metabolism of tricyclic antidepressants. Cell Mol Neurobiol 1999;19:373–409.
9. Kurpius MP, Alexander B. Rates of in vivo methylation of desipramine and nortriptyline. Pharmacotherapy 2006;26:505–10.
10. Banks DB, Chan GN, Evans RA, Miller DS, Cannon RE. Lysophosphatidic acid and amitriptyline signal through LPA1R to reduce P-glycoprotein transport at the blood-brain barrier. J Cereb Blood Flow Metab 2018;38:857–68.
11. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, et al. Pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther 2012;92:414–7.
12. Gillman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. Br J Pharmacol 2007;151:737–48.
13. Sandoz Inc. Medication Guide: Amitriptyline Hydrochloride Tablets, USP. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/085966s095,085969s084,085968s096,085971s075,085967s076,085970s072lbl.pdf. Acessed on 31. January 2020.
14. Jankovic J, Tolosa E. Parkinson's Disease and Movement Disorders. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.
15. American Psychiatric Association. DSM–IV: Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: APA; 1994.
16. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–45.
17. Friedman LM, Furberg CD, DeMets D, Reboussin DM, Granger CB. Fundamentals of Clinical Trials. Cham, Switzerland: Springer; 2015.
18. Bockner S. Side-effect of amitriptyline. Br Med J 1965;1:1188.
19. Witton K. Severe toxic reaction to combined amitriptyline and thioridazine. Am J Psychiatry 1965;121:812–3.
20. Darcourt G, Fadeuilhe A, Lavagna J, Cazac A. Three cases of action myoclonus during treatment with imipramine and amitriptyline. Rev Neurol (Paris) 1970;122:141–2.
21. Burks JS, Walker JE, Rumack BH, Ott JE. Tricyclic antidepressant poisoning: reversal of coma, choreoathetosis, and myoclonus by physostigmine. JAMA 1974;230:1405–7.
22. National Drugs Advisory Board, Ireland. Reports of Side Effects Associated with the Use of Drugs 1968–1975. Dublin: Charles Lucas House; 1976.
23. National Drugs Advisory Board, Ireland. Reports of Side Effects Associated with the Use of Drugs 1976. Dublin: Charles Lucas House; 1977.
24. Fann WE, Sullivan JL, Richman BW. Dyskinesias associated with tricyclic antidepressants. Br J Psychiatry 1976;128:490–3.
25. Lippmann S, Moskovitz R, O'Tuama L. Tricyclic-induced myoclonus. Am J Psychiatry 1977;134:90–1.
26. Lippmann S, Tucker D, Wagemaker H, Schulte T. A second report of tricyclic-induced myoclonus. Am J Psychiatry 1977;134:585–6.
27. Quader SE. Dysarthria: an unusual side effect of tricyclic antidepressants. Br Med J 1977;2:97.
28. Schatzberg AF, Cole JO, Blumer DP. Speech blockage: a tricyclic side effect. Am J Psychiatry 1978;135:600–1.
29. Sholomskas AJ. Speech blockage in young patients taking tricyclics. Am J Psychiatry 1978;135:1572–3.
30. Woogen S, Graham J, Angrist B. A tardive dyskinesia-like syndrome after amitriptyline treatment. J Clin Psychopharmacol 1981;1:34–6.
31. Finder E, Lin KM, Ananth J. Dystonic reaction to amitriptyline. Am J Psychiatry 1982;139:1220.
32. Krishnan KR, France RD, Ellinwood Jr EH. Tricyclic-induced akathisia in patients taking conjugated estrogens. Am J Psychiatry 1984;141:696–7.
33. Schmidt LG, Grohmann R, Helmchen H, Langscheid-Schmidt K, Müller-Oerlinghausen B, Poser W, et al. Adverse drug reactions. An epidemiological study at psychiatric hospitals. Acta Psychiatr Scand 1984;70:77–89.

34. Koller WC, Musa MN. Amitriptyline-induced abnormal movements. Neurology 1985;35:1086.
35. Gangat AE, Luiz HA, Kajee AH, Ibrahim NI, Simpson MA. Tricyclic-induced acute tardive dyskinesia. A case report. S Afr Med J 1987;71:729.
36. Garvey MJ, Tollefson GD. Occurrence of myoclonus in patients treated with cyclic antidepressants. Arch Gen Psychiatry 1987;44:269–72.
37. Lee HK. Dystonic reactions to amitriptyline and doxepin. Am J Psychiatry 1988;145:649.
38. Foerstl J, Hohagen F, Hewer W, Pohlmann-Eden B. Another case of Creutzfeldt-Jakob like syndrome due to antidepressant toxicity. J Neurol Neurosurg Psychiatry 1989;52:920.
39. Miller LG, Jankovic J. Neurologic approach to drug-induced movement disorders: a study of 125 patients. South Med J 1990; 83:525–32.
40. Ornadel D, Barnes EA, Dick DJ. Acute dystonia due to amitriptyline. J Neurol Neurosurg Psychiatry 1992;55:414.
41. Nisijima K, Shimizu M, Abe T, Ishiguro T. A case of serotonin syndrome induced by concomitant treatment with low-dose trazodone and amitriptyline and lithium. Int Clin Psychopharmacol 1996;11:289–90.
42. Maher J, Choudhri S, Halliday W, Power C, Nath A. AIDS dementia complex with generalized myoclonus. Mov Disord 1997;12:593–7.
43. Spigset O, Hedenmalm K, Dahl ML, Wiholm BE, Dahlqvist R. Seizures and myoclonus associated with antidepressant treatment: assessment of potential risk factors, including CYP2D6 and CYP2C19 polymorphisms, and treatment with CYP2D6 inhibitors. Acta Psychiatr Scand 1997;96:379–84.
44. Suzuki T, Kurita H, Hori T, Sasaki M, Baba A, Shiraishi H, et al. The Pisa syndrome (pleurothotonus) during antidepressant therapy. Biol Psychiatry 1997;41:234–6.
45. Vandel P, Bonin B, Leveque E, Sechter D, Bizouard P. Tricyclic antidepressant-induced extrapyramidal side effects. Eur Neuropsychopharmacol 1997;7:207–12.
46. Le Doze F, Moulin M, Defer GL. Meige's syndrome in a patient treated with ranitidine. Mov Disord 1999;14:175–7.
47. Perry NK. Venlafaxine-induced serotonin syndrome with relapse following amitriptyline. Postgrad Med J 2000;76:254–6.
48. Yotsui H, Matsunaga M, Katori K, Kohno S, Higa K. Extrapyramidal reactions after epidural droperidol. Masui 2000;49:1152–4.
49. Gourzis P, Polychronopoulos P, Argyriou AA, Bakalidou C, Beratis S. Induction of the rabbit syndrome following coadministration of paroxetine, perphenazine, and amitriptyline. Clin Neuropharmacol 2004;27:299–300.
50. Choi JP, Park SS, Park JS, Na SJ. A case of myoclonus presenting as a side effect of amitriptyline. J Korean Soc Clin Toxicol 2006;4:155–7.
51. Simpson SM, Whitfield A. An unusual cause of movement disorder in a young man with penile carcinoma. J Pain Symptom Manage 2007;33:656–8.
52. Callista G, Di Emidio G. A case of "rabbit syndrome" induced by amitriptyline. Eur Neuropsychopharmacol 2014;24:S740.
53. Kim YD, Yum KS. Tricyclic antidepressant-induced myoclonus: case report and literature review. Mov Disord 2009;24:70.
54. Madhusoodanan S, Alexeenko L, Sanders R, Brenner R. Extrapyramidal symptoms associated with antidepressants—a review of the literature and an analysis of spontaneous reports. Ann Clin Psychiatry 2010; 22:148–56.
55. Pawar PS, Woo DA. Extrapyramidal symptoms with concomitant use of amitriptyline and amiodarone in an elderly patient. Am J Geriatr Pharmacother 2010;8:595–8.
56. Bondon-Guitton E, Perez-Lloret S, Bagheri H, Brefel C, Rascol O, Montastruc J-L. Drug-induced Parkinsonism: a review of 17 years' experience in a regional pharmacovigilance center in France. Mov Disord 2011;26:2226–31.
57. Cappuccio G, Brunetti-Pierri N, Terrone G, Romano A, Andria G, Del Giudice E. Low-dose amitriptyline-induced acute dystonia in a patient with metachromatic leukodystrophy. JIMD Rep 2013;9:113–6.
58. Sreejayan K, Praharaj SK. Myoclonus associated with disulfiram. J Neuropsychiatry Clin Neurosci 2013;25:E37–9.
59. Gedam SR, Goyal A, Shivji IA. Acute dystonia with concomitant use of amitriptyline and paroxetine. Open J Psychiatry Allied Sci 2017;8:84–6.
60. Hiremath SB, Desai M. Amitriptyline induced cervical dystonia. J Sci Soc 2016;43:38–40.
61. Philips CA, Augustine P. Amitriptyline induced tardive dyskinesia in a patient with cirrhotic Parkinsonism. India J Med Specialities 2017;8:86–8.
62. Paoletti FP, Di Gregorio M, Calabresi P, Parnetti L. Drug-induced Creutzfeldt-Jakob disease-like syndrome: early CSF analysis as useful tool for differential diagnosis. BMJ Case Rep 2018;11:e224314.
63. Hunter CB, Kenney C, Mejia N, Davidson A, Jankovic J. Medications Associated with the Onset of Tardive Dyskinesia. Available at: https://www.bcm.edu/neurology/pdf/poster_pdcmdc_Meds_TDysk_ANA.pdf. Accessed on 31 January 2020.
64. Kumar M, Vijayavarman V, Singh AK. Acute extrapyramidal symptoms associated with concomitant use of amitriptyline and oral contraceptive pills: a case report. J Med Sci Clin Res 2019; 7:1024–6.
65. Mithun S. Amitriptyline induced acute dyskinesia. Int J Health Sci Pharmacy 2019;3:40–2.
66. Caviness JN, Brown P. Myoclonus: current concepts and recent advances. Lancet Neurol 2004;3:598–607.
67. Gupta A, Lang AE. Drug-induced cranial myoclonus. Mov Disord 2010;25:2264–5.
68. Sutter R, Ristic A, Rüegg S, Fuhr P. Myoclonus in the critically ill: diagnosis, management, and clinical impact. Clin Neurophysiol 2016;127:67–80.
69. Jiménez-Jiménez FJ, Puertas I, de Toledo-Heras M. Drug-induced myoclonus: frequency, mechanisms and management. CNS Drugs 2004;18:93–104.
70. Lhermitte F, Peterfalvi M, Marteau R, Gazengel J, Serdaru M. Pharmacological analysis of a case of postanoxic intention and action myoclonus. Rev Neurol (Paris) 1971;124:21–31.
71. Giménez-Roldán S, Mateo D, Muradas V, De Yebenes JG. Clinical, biochemical, and pharmacological observation in a patient with postasphyxic myoclonus: association to serotonin hyperactivity. Clin Neuropharmacol 1988;11:151–60.
72. Klawans Jr HL, Goetz C, Weiner WJ. 5-hydroxytryptophan-induced myoclonus in guinea pigs and the possible role of serotonin in infantile myoclonus. Neurology 1973;23:1234–40.
73. Lepping P, Delieu J, Mellor R, Williams JHH, Hudson PR, Hunter-Lavin C. Antipsychotic medication and oxidative cell stress: a systematic review. J Clin Psychiatry 2011;72:273–85.
74. Blandina P, Munari L, Provensi G, Passani MB. Histamine neurons in the tuberomamillary nucleus: a whole center or distinct subpopulations? Front Syst Neurosci 2012;6:33.
75. Bird ED, Iversen LL. Neurochemical findings in Huntington's chorea. Essays Neurochem Neuropharmacol 1977;1:177–95.
76. Cloud LJ, Jinnah HA. Treatment strategies for dystonia. Expert Opin Pharmacother 2010;11:5–15.
77. Rissardo JP, Caprara ALF. Comment: dystonia and asterixis in acute thalamic infarct: proposed mechanism. Ann Mov Disord 2019;2:138–9.

78. Eu KM, Tan LCS, Tan ARJ, Seah ISH, Lau PN, Li W, et al. Spectrum and burden of movement disorder conditions in a tertiary movement disorders centre—a 10-year trend. Ann Acad Med Singapore 2014;43:203–8.
79. Reed MC, Nijhout HF, Best J. Computational studies of the role of serotonin in the basal ganglia. Front Integr Neurosci 2013;7:41.
80. Benarroch EE. Serotonergic modulation of basal ganglia circuits: complexity and therapeutic opportunities. Neurology 2009; 73:880–6.
81. Miguelez C, Morera-Herreras T, Torrecilla M, Ruiz-Ortega JA, Ugedo L. Interaction between the 5–HT system and the basal ganglia: functional implication and therapeutic perspective in Parkinson's disease. Front Neural Circuits 2014;8:21.
82. Hajós M, Gartside SE, Sharp T. Inhibition of median and dorsal raphe neurones following administration of the selective serotonin reuptake inhibitor paroxetine. Naunyn Schmiedebergs Arch Pharmacol 1995;351:624–9.
83. Vertes RP. A PHA-L analysis of ascending projections of the dorsal raphe nucleus in the rat. J Comp Neurol 1991;313:643–68.
84. Chua HC, Tan AK, Venketasubramanian N, Tan CB, Tjia H. Palatal myoclonus—a case report. Ann Acad Med Singapore 1999;28:593–5.
85. Hurd YL, Suzuki M, Sedvall GC. D1 and D2 dopamine receptor mRNA expression in whole hemisphere sections of the human brain. J Chem Neuroanat 2001;22:127–37.
86. Dalley JW, Mar AC, Economidou D, Robbins TW. Neurobehavioral mechanisms of impulsivity: fronto-striatal systems and functional neurochemistry. Pharmacol Biochem Behav 2008;90:250–60.
87. Vandel P, Bonin B, Vandel S, Sechter D, Bizouard P. CYP 2D6 PM phenotype hypothesis of antidepressant extrapyramidal side-effects. Med Hypotheses 1996;47:439–42.
88. Patatanian E, Claborn MK. Drug-induced restless legs syndrome. Ann Pharmacother 2018;52:662–72.
89. Baughman KR, Bourguet CC, Ober SK. Gender differences in the association between antidepressant use and restless legs syndrome. Mov Disord 2009;24:1054–9.
90. Appel NM, Elde RP. The intermediolateral cell column of the thoracic spinal cord is comprised of target-specific subnuclei: evidence from retrograde transport studies and immunohistochemistry. J Neurosci 1988;8:1767–75.
91. Mitchell UH, Obray JD, Hunsaker E, Garcia BT, Clarke TJ, Hope S, et al. Peripheral dopamine in restless legs syndrome. Front Neurol 2018;9:155.

Commentary

Artificial Intelligence and Medical Innovation

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Artificial intelligence (AI) is considered to be at the cutting edge of the 4th Industrial Revolution, and is part of a wave of technologies that will lead to the unprecedented fusion of the physical, digital and biological realms. As a result of the convergence brought about by technologies such as AI, biomedical engineering, robotics and nanotechnology, every facet of human society from health to industry, living environments and education is expected to be reshaped in the decades ahead. That being said, there is a need to balance its potential and impact against rising concerns such as transparency, privacy and human-centric decision-making.

AI and Healthcare

Healthcare is identified as one of the fields that will be profoundly impacted by AI. One of the reasons given is the exponential rate of growth in medical data. In 2013, 153 exabytes of healthcare data were generated. This number is estimated to hit 2314 exabytes in the year 2020, a projected rate of growth of 48% a year (1 exabyte is equivalent to 1 billion gigabytes, or 5 times the data of all printed materials in the world!).[1]

Other key drivers for the adoption of AI in healthcare include a rapidly ageing population, surge in chronic diseases in developed and developing countries, growing demand for skills and manpower in the health sector and the need to control spiralling health costs.

AI Gains Global Attention

The term "Artificial Intelligence" was coined by John McCarthy, a computer scientist, in 1956[2] and the associated term "Machine Learning" was introduced by Arthur Samuel in 1959.[3]

For many years, AI and self-learning machines remained within the speculative realm of science fiction. AI first emerged into the public consciousness in 1996 after former world chess champion, Garry Kasparov, was beaten in 1 of 6 games by the chess-playing computer—Deep Blue—developed by IBM, and again in 1997. In 2015, AI gained global attention after AlphaGo, a computer application developed by Google to play the board game Go, emerged victorious against a human Go champion. Compared to chess, it was widely thought that Go would be too difficult for a computer to master. With these victories, the world finally woke up to the astonishing power and sophistication that AI technologies have to offer.

Both events, which took place 2 decades apart from one another, also demonstrated the rapid pace of technological advancement in AI. Deep Blue was a purpose-built computer that achieved its winning feat through a combination of clever algorithms and brute-force computing power.[4] It was capable of performing 200 million moves a second, or 36 billion positions in 3 minutes, which was the time allocated for a single move to be made under chess tournament conditions.

In 2016, AlphaGo deployed AI at a higher level of sophistication. Unlike Deep Blue, AlphaGo employed learning or—in technical jargon—deep learning. After being fed with 30 million Go moves, it could play against itself and build its own databank of knowledge and experience, thereby learning and enriching that databank. Computing power and the advent of more effective algorithms made AlphaGo different from Deep Blue. Its core technology was the use of artificial neural networks (or sophisticated algorithms) to perform deep learning. Deep learning is a subset of machine learning, where neural networks learn from large amounts of data and try to emulate how the human brain learns from experience. The design of neural networks was loosely modelled after the human brain and its processes, which typically consists of millions of interconnected neurons communicating and transmitting information to one another.[5]

Before AlphaGo, it was thought that AI would not be able to master the board game Go; in fact, after Deep Blue's victory in 1997, it was thought that it would be another 100 years before a computer could play Go at a sufficiently high level.[6]

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AI: The New "OS" for Healthcare

Today, AI is used in diverse industries ranging from online commerce to logistics, traffic management and weather forecasting. In healthcare, AI is viewed as a key enabling technology that can unleash new models of care across primary, secondary and tertiary levels. The projected role of AI in healthcare has become so central that it has since been described as the new "OS" in healthcare of the future.[7]

A key strength of AI is in pattern recognition and detection, particularly seen in the fields of radiology[8] and ophthalmology.[9] Promising trials have been conducted—including those in Singapore[10]—where AI and machine learning were used to detect and diagnose a wide range of diseases and conditions from cancers to brain injuries, chronic illnesses and even depression. In some cases, the AI rate of accuracy matched—and possibly surpassed—that of human experts.[11]

Another strength of AI is that of predictive analytics. AI can scan vast amounts of biomedical, clinical and patient data and information to identify subjects who have a family history of hereditary diseases or those at increased risk of a chronic disease.[12] Predictive analytics can trigger early intervention, which can then be paired with personalised care. With improved processing time, there is greater optimisation of resources and better load capacity management in a healthcare system.[13]

AI and robotics complement each other highly, and the results are applications that range from robot-assisted surgery to care solutions for the elderly. The Japanese conglomerate, Sony, recently launched a robotic dog, Aibo, that was equipped with cameras, artificial intelligence and Internet connectivity. Aibo can be used to monitor the elderly, children and even pets.[14] AI and robotics could well become the transformative key that can provide "caring in place" solutions for the growing elderly population. With the advent of fifth generation—or 5G—technologies, surgical procedures can even be performed by surgeons across locations.[15]

AI can also play a greater role in medical learning and training through the simulation of naturalistic scenarios, access to vast databases on cases and conditions and customisable learning situations based on active, real-time feedback.[15]

Researchers are also exploring the possibilities and potential of AI at the microscopic and even nano levels. Smart biosensors are envisaged to be powered by AI that are capable of taking highly accurate medical images and to provide live feeds of compounds and chemicals traversing through the human body. Other possibilities include the use of micro-scale bio-vehicles in drug administration that provide precise targeting of locations in the required dosages.[16–8]

Strengths and Limitations of AI

Although AI is expected to play a central role in future, it is important to have a balanced view of its strengths and limitations. With this understanding, there can be better appreciation of the critical role that human decisions will continue to play even as healthcare and other sectors increasingly utilise and deploy AI in various roles and functions.

A major advantage of AI is that it can process and analyse information on an unprecedented scale and speed. The computational, quantitative and analytical capabilities of AI have surged beyond the threshold of human abilities. AI can plough through enormous troves of data—past and present—from multiple sources in the search for a solution. AI also excels at spotting patterns and anomalies and can flag them for further study or to generate new ideas.

Unlike humans, AI does not suffer from decision fatigue. Consequently, this improves speed and accuracy in decision-making[19] that can prove to be vital in situations such as time-sensitive healthcare diagnosis. These are the powerful advantages of AI, but there are also significant shortfalls and blind spots in current AI technology.

A major roadblock to the adoption of AI in healthcare is the issue of the "black box" problem. Because of its self-adjusting algorithms and statistical weighing computations, AI is not able to explain—in a transparent manner—how a decision or option was derived. In healthcare, the relationship of trust between patients and healthcare professionals is of paramount importance, and this is maintained and supported by exacting standards of accountability and transparency.

Another limitation of AI is the need to ensure that the data and information fed into an AI engine is free from bias or defect. When the datasets are flawed or when its programmes or algorithms contain biases or filters that skew results or outcomes, the reinforcing and compounding nature of AI will magnify these defects—and perhaps exponentially—over time.

Finally, AI still lacks the unique cognitive capabilities of humans, such as the ability to generalise or abstract relationships from limited data or to transfer insights and knowledge from one domain to another. In the field of linguistics, AI also struggles to define symbols, concepts and their associative meanings (such as the

meaning of puppy love) although intense research is ongoing to address this issue.

Humans and AI: a Synergistic Pairing

With a fuller understanding of the capabilities and limitations of AI, one can then turn to a consideration of how the power of AI can be harnessed to synergise with the unique attributes of humans.

Many decisions are made when there is imperfect information, uncertainty and unpredictability. Under these circumstances, an intuitive or "gut decision" approach is often used. Although widely described as lacking rationality, a more accurate description of this approach would be decision-making that is based on a blend of imagination, sensitivity, experience, extrapolation and judgement. It is about analysing and understanding the situation at a deeper level of perception and looking at the world with an "abstracted and holistic view".[20] It is a very unique human ability.

Another aspect of human decision-making involves dealing with "equivocality". Put simply, in complex scenarios, interested parties who have different agendas and interests may differ considerably in their interpretations of decisions.[20] Human actors must negotiate diverse—and sometimes conflicting—needs, and this requires deep social intelligence and sensitivity to both formal and informal contexts to build a common ground.

Leadership is another human activity that operates at both formal and informal levels. Leadership is often a synthesis of analytic rigour, creative and original thinking and social and emotional intelligence. While AI can be used as a powerful tool to analyse data and patterns, the future rarely unfolds according to strictly prescriptive and rational terms; instead, leaders must provide context, empathy and an integrated, holistic perspective even as their organisations adapt to changing circumstances.

New Competencies and Evolving Roles

For an AI-human symbiosis to achieve its full impact, several approaches can be adopted. The first approach is to raise AI literacy and competency across the board throughout an organisation. A foundational understanding of how AI technologies work will facilitate informed discussion on how AI can be integrated into individual and organisational processes and requirements. AI literacy will also increase confidence and reduce anxiety in adapting to—and exploring—new possibilities as technologies advance.

Another major area concerns the redesign or reimagination of roles, scope and processes in the workplace that involves 2 components: distinguishing and harmonising the complementary capabilities of human intelligence and AI. Just as a greater understanding of AI technologies can sharpen the analytical skills of human agents, AI can enhance its utility through greater interaction and feedback from more human interactions. For example, an interdisciplinary team that harnessed the power of CURATE.AI—an AI platform—was able to continuously identify the optimal doses of a drug treatment programme for the successful treatment of cancer and other diseases.[21,22]

The second approach is closely related to the enhancement of human attributes such as holistic thinking, emotional intelligence and imaginative problem-solving. When their capabilities in these areas are strengthened, human actors will be better placed to reap greater synergy and positive outcomes from their partnership with AI.

The third approach is to relook current data framework. Data is now a new "resource", and it is a particularly important one in AI. Data is the "input" that is needed to drive AI. When the data is corrupted, the outcomes from AI would be affected. This is a manifestation of the "garbage in and garbage out" syndrome. Thus, it is important to maintain data collation and integrity.

Finally, AI is a powerful technology and efforts must be made to ensure that it is beneficently harvested for human benefit. Recently, Singapore has articulated her AI Governance Framework[23] which is a forward-looking and human-centric model that stresses technological advancement for the benefit of society and allows adaptability and flexibility as the AI landscape continues to evolve.

Ultimately, AI is a tool and a technology. It is also one of the most powerful inventions created by humans. In coming years, its transformative potential will undoubtedly reshape critical sectors such as healthcare. However, humans will still retain the autonomy—and responsibility—to ensure its fair and justifiable use to address human challenges and improve the well-being of society.

REFERENCES

1. Stanford University School of Medicine. Stanford Medicine 2017 Health Trends Report: Harnessing the Power of Data in Health. Available at: https://med.stanford.edu/content/dam/sm/sm-news/

documents/fordMedicineHealthTrendsWhitePaper2017.pdf. Accessed on 19 April 2020

2. Ray S. History of AI. Towards Data Science, 11 August 2018. Available at: https://towardsdatascience.com/history-of-ai-484a86fc16ef. Accessed on 19 April 2020.
3. Pesapane F, Codari M, Sardanelli F. Artificial intelligence in medical imaging: threat or opportunity? Radiologists again at the forefront of innovation in medicine. Eur Radiol Exp 2018;2:35.
4. Press G. The brute force of IBM Deep Blue and Google DeepMind. Forbes, 7 February 2018. Available at: https://www.forbes.com/sites/gilpress/2018/02/07/the-brute-force-of-deep-blue-and-deep-learning/#723e1ed149e3. Accessed on 19 April 2020.
5. Society for Neuroscience. The Neuron. BrainFacts, 1 April 2012. Available at: http://www.brainfacts.org/Brain-Anatomy-and-Function/Anatomy/2012/The-Neuron. Accessed on 19 April 2020.
6. Johnson G. To test a powerful computer, play an ancient game. The New York Times, 29 July 1997. Available at: https://www.nytimes.com/1997/07/29/science/to-test-a-powerful-computer-play-an-ancient-game.html?pagewanted=all. Accessed on 19 April 2020.
7. Sham J. Artificial intelligence in health. Accenture Health, 8 February 2019. Available at: https://www.accenture.com/sg-en/insights/public-service/artificial-intelligence-health. Accessed on 19 April 2020.
8. Liew CJ, Krishnaswamy P, Cheng LT, Tan CH, Poh AC, Lim TC. Artificial intelligence and radiology in Singapore: championing a new age of augmented imaging for unsurpassed patient care. Ann Acad Med Singapore 2019;48:16–24.
9. Ting DSW, Lee AY, Wong TY. An ophthalmologist's guide to deciphering studies in artificial intelligence. Ophthalmology 2019;126:1475–9.
10. Kwang K. When every second counts: using AI to assess brain injuries could save lives. Channel NewsAsia, 26 June 2019. Available at: https://www.channelnewsasia.com/news/singapore/when-every-second-counts-using-ai-to-assess-brain-injuries-could-11655792. Accessed on 19 April 2020.
11. Laifenfeld D. Harnessing AI to revolutionize cancer diagnosis. IBEX, 20 October 2018. Available at: https://ibex-ai.com/blog/ai-to-revolutionize-cancer-diagnosis/. Accessed on 19 April 2020.
12. Hamet P, Tremblay J. Artificial intelligence in medicine. Metabolism 2017;69:S36–40.
13. Krittanawong C. The rise of artificial intelligence and the uncertain future for physicians. Eur J Intern Med 2018;48:e13–4.
14. AFP. Paw patrol: Sony's Robocop dog aibo keeps an eye on the elderly, children and pets at home. The Straits Times, 23 Janaury 2019. Available at: https://www.straitstimes.com/asia/east-asia/paw-patrol-sonys-robocop-dog-aibo-keeps-an-eye-on-the-elderly-children-and-pets-at. Accessed on 19 April 2020.
15. PwC Global. No longer science fiction, AI and robtics are transforming healthcare. Available at: https://www.pwc.com/gx/en/industries/healthcare/publications/ai-robotics-new-health/transforming-healthcare.html. Accessed on 19 April 2020.
16. Marr B. How is AI used in healthcare—5 powerful real-world examples that showed the latest advances. Forbes, 27 July 2018. Available at: https://www.forbes.com/sites/bernardmarr/2018/07/27/how-is-ai-used-in-healthcare-5-powerful-real-world-examples-that-show-the-latest-advances/#4cb0d0735dfb. Accessed on 19 April 2020.
17. Critchley L. The convergence of AI and nanotechnology. Nano, 22 August 2018. Available at: https://nano-magazine.com/news/2018/8/22/the-convergence-of-ai-and-nanotechnology. Accessed on 19 April 2020.
18. Brown M. The future of medicine is at the nanoscale. Engineering.com, 15 February 2019. Available at: https://www.engineering.com/DesignerEdge/DesignerEdgeArticles/ArticleID/18561/The-Future-of-Medicine-is-at-the-Nanoscale.aspx. Accessed on 19 April 2020.
19. Cooper P. Why AI drives better business decision-making. Salesforce, 3 November 2017. Available at: https://www.salesforce.com/blog/2017/11/why-ai-drives-better-business-decision-making.html. Accessed on 19 April 2020.
20. Jarrahi MH. Artificial intelligence and the future of work: human-AI symbiosis in organizational decision making. Business Horizons 2018;61:577–86.
21. Londhe VY, Bhasin B. Artificial intelligence and its potential in oncology. Drug Discov Today 2019;24:228–32.
22. Blasiak A, Khong J, Kee T. CURATE.AI: optimizing personalized medicine with artificial intelligence. SLAS Technol 2020;25:95–105.
23. Tan S. Singapore releases framework on how AI can be ethically used. The Straits Times, 23 January 2019. Available at: https://www.straitstimes.com/singapore/singapore-releases-model-governance-framework-for-ai. Accessed on 19 April 2020.

Commentary

Artificial Intelligence: A Singapore Response

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The world is in the midst of a new industrial transformation with the rise of artificial intelligence (AI).[1] Physicians and health systems will increasingly need to adapt amidst skyrocketing demand for health services due to multiple converging socioeconomic trends that include an ageing population in many countries. This trend is exacerbated by heightened expectations as the quality of health services improves and life expectancy increases. As the number of young health professionals and workers is reduced, AI shows great potential to disrupt the delivery of health services and to revolutionalise patient treatment to meet this need.

Application of AI-Augmented Healthcare

AI has been used in health services since the 1970s and has gone through several hype-and-bust cycles. Nonetheless, the convergence of several trends in the world today heralds an exciting new era in the use of AI. These include an exponential increase in computing power, rise in investment capital, explosion in data creation and capture and development of deep learning (DL) techniques which utilised multilayered neural networks to create conditions that improve accuracy of AI detection. In 2014, GoogLeNet—a convolutional neural network—classified 15 million Internet images into >20,000 categories at near-human accuracy that caused much worldwide sensation.[2]

Since DL neural networks are not limited by human fatigue and are able to process large amounts of information round the clock, they can be deployed to perform a large variety of repetitive, cognitive tasks across the entire health sector. The future of health servcies that are augmented by AI systems holds immense potential, and researchers in Singapore are well-placed to participate in their creation.[1]

Radiologists are early adopters of AI in medicine since they have been using DL to detect and classify pneumonia,[3] tuberculosis[4,5] and fractures[6] on radiographs, and for tumour auto-segmentation and imaging workflow optimisation.[7] DL algorithms are now used to upsample data from low-dose computed tomography (CT) studies to yield high-quality images that are comparable to conventional CT scans, thereby reducing radiation exposure in patients.[8]

AI-based image analysis solutions have also been deployed in pathology laboratories to predict tumours that result in poorer outcomes.[9] After a team from National Neuroscience Institute used DL to classify brain glioma specimens into histological grades, they proceeded to adapt their work by using it to classify breast histology images, thereby showing the use of transfer learning across tissue types.

Researchers in Singapore National Eye Centre (SNEC) have also used DL systems to detect diabetic retinopathy in digital retinal photography with excellent accuracy.[10] Such efforts have been extended to include other conditions such as glaucoma and age-related macular degeneration.[11] They are also used in under-resourced African countries to revolutionalise eye screening and to reduce the incidence of preventable blindness.[12]

Similar technologies can also predict cardiovascular risk factors from retinal images, an outcome that was not previously thought possible by human readers.[13] Researchers at National Heart Centre Singapore have assimilated demographic, clinical, electrocardiographic and imaging data to diagnose coronary artery disease by using AI.[14] Predictive analytics that aggregate data from diverse sources, including medical history and environmental parameters, can also have the potential to revolutionalise public health and preventive medicine.

AI to Augment Health Professionals

Despite its immense potential, a few limitations that are inherent in AI need to be addressed before it can be implementated on a wide scale. The value proposition of DL lies in its ability to draw its own conclusion and

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method of interpretation. However, its decision-making logic is often not clear—the well known "Black Box" problem. Thus, the opacity of AI decision-making presents potentially serious accountability issues. To complicate matters, it is now possible to develop adversarial systems that can corrupt raw imaging data to confuse AI into making erroneous diagnoses.[15] Consequently, clinically trained human oversight and validation are still indispensable in the prevention of poor patient outcomes.

Another limitation of DL is the dependence on a large amount of data that is well annotated and of good quality in an effective neural network. Experienced clinicians are needed to select, validate and label data precisely and accurately, and to ensure that DL systems use external data that is applicable to local patient populations. Even after the adoption of AI, doctors in Singapore need to continually audit, retrain and revalidate AI applications.

Finally, clinical AI solutions that are currently available have been designed for niche implementation and to focus on specific tasks; a general AI solution does not appear to be on the horizon at any time soon. Therefore, a wide gamut of different but specific AI tools may be needed for different clinical scenarios. Health professionals will soon need to also help patients navigate these complexities and make sense of AI outputs. Consequently, there is a need to customise medical systems that can allow judicious implementation of AI algorithms in controlled clinical environments to ensure safe and effective care for patients in Singapore.[7] This is true of each stage in the development of AI, from the identification of real clinical needs at the inception of a DL system to clinical data labelling, system validation, implementation in the clinical setting, helping patients to make sense of their data and, finally, audit of pooled outcome measures.

A Bright, Not Dystopian, Future

Health professionals who once entertained unfounded fears of being replaced by AI can now look forward to embracing the potential that an AI-augmented health system brings. In a recent survey of attitudes towards AI among radiology residents and faculty in Singapore, most respondents were confident that human radiologists will not be replaced. They were also motivated to advance their knowledge of AI and to become involved in related research.[16]

In the brave new world of AI-augmented health services, health professionals must adapt to their evolving role in patient care. Traditional health roles will move from mere technical expertise in diagnosis and therapy to a greater emphasis on patient-centric care that focuses on the emotive and less tangible needs of patients and their families. AI will also empower patients to be active participants in care provision, as real-time data collected from their wearable or implantable sensors can alert doctors to actionable knowledge and contribute to a growing pool of training data for AI systems. AI systems can even be used to operate robotics and smart machinery to automate routine health procedures, thereby freeing up limited manpower to provide more holistic patient care. As more repetitive clerical work is handled by intelligent computer systems, there is more time to address the ideas, concerns and expectations of patients and to become more humanistic in clinical practice.

On the flip side, a dystopian future can be imagined: unbridled, error-prone AI systems that are unchecked by ethics, operating in a workspace cohabited with a burnt-out, demoralised and disempowered workforce. Such a scenario does not benefit patients or health systems. As the provision of health servcies becomes more intricately woven with the flow of data and information, health providers must be seen as guardians of patients' information and as indispensable guides to help make sense of countless—and occasionally unintelligible—reports. Doctors must raise their data literacy and competency to manage health information, and to combine bedside knowledge with bench-side capabilities to create quality AI-augmented health solutions.[17] Singapore can be at the forefront of designing and implementing ethical and robust data strategies across health systems to ensure the data and interests of patients are protected.[18] Ethics, professionalism and advocacy may become even more vital to good clinical practice.

In conclusion, the health sector is on the cusp of a new and exciting age. Health professionals must strengthen their mindsets, practice and capabilities. Singapore can lead the way in the implementation of real AI solutions that benefit patients and champion their interests in this brave new age. Patients may not need a sophisticated AI who knows, but they definitely need an AI-augmented doctor who cares.

REFERENCES

1. Tan EC. Artificial intelligence and medical innovation. Ann Acad Med Singapore 2020;49:252–5.
2. Russakovsky O, Deng J, Su H, Krause J, Satheesh S, Ma S, et al. ImageNet Large Scale Visual Recognition Challenge. arXiv, 30 January 2015. Available at: http://arxiv.org/abs/1409.0575. Accessed on 26 August 2019.
3. Rajpurkar P, Irvin J, Zhu K, Yang B, Mehta H, Duan T, et al. CheXNet: Radiologist-Level Pneumonia Detection on Chest X-Rays with Deep

Learning. arXiv, 25 December 2017. Available at: http://arxiv.org/abs/1711.05225. Accessed on 2 April 2019.

4. Ting DSW, Yi PH, Hui F. Clinical applicability of deep learning system in detecting tuberculosis with chest radiography. Radiology 2018;286:729–31.
5. Lakhani P, Sundaram B. Deep learning at chest radiography: automated classification of pulmonary tuberculosis by using convolutional neural networks. Radiology 2017;284:574–82.
6. Thian YL, Li Y, Jagmohan P, Sia D, Chan VEY, Tan RT. Convolutional neural networks for automated fracture detection and localization on wrist radiographs. Radiol Artif Intell 2019;1:e180001.
7. Liew CJ, Cheng LT, Tan CH, Poh AC, Lim TC. Artificial intelligence and radiology in Singapore: championing a new age of augmented imaging for unsurpassed patient care. Ann Acad Med Singapore 2019;48:9.
8. Shan H, Padole A, Homayounieh F, Kruger U, Khera RD, Nitiwarangkul C, et al. Competitive performance of a modularized deep neural network compared to commercial algorithms for low-dose CT image reconstruction. Nature Machine Intelligence 2019;1:269–76.
9. Ker J, Bai Y, Lee HY, Rao J, Wang L. Automated brain histology classification using machine learning. J Clin Neurosci 2019;66:239–45.
10. Ting DSW, Cheung CYL, Lim G, Tan GSW, Quang ND, Gan A, et al. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. JAMA 2017;318:2211–23.
11. Ting DS, Rim TH, Choi YS, Ledsam JR. Deep learning in medicine. Are we ready? Ann Acad Med Singapore 2019;48:4.
12. Bellemo V, Lim ZW, Lim G, Quang DN, Yuchen X, Yip MYT, et al. Artificial intelligence using deep learning to screen for referable and vision-threatening diabetic retinopathy in Africa: a clinical validation study. The Lancet Digital Health 2019;1:e35–44.
13. Ting DSW, Wong TY. Eyeing cardiovascular risk factors. Nat Biomed Eng 2018;2:140–1.
14. Mandal I, Sairam N. Accurate prediction of coronary artery disease using reliable diagnosis system. J Med Syst 2012;36:3353–73.
15. Papernot N, McDaniel P, Goodfellow I, Jha S, Celik ZB, Swami A. Practical Black-Box Attacks Against Machine Learning. In: Proceedings of the 2017 ACM on Asia Conference on Computer and Communications Security. ASIA CCS '17. New York, USA; ACM:2017:506–19.
16. Ooi S, Makmur A, Soon Y, Fook-Chong S, Liew C, Sia SY, et al. Attitudes toward artificial intelligence in radiology with learner needs assessment within radiology residency programmes: a national multi-programme survey. Singapore Med J 2019. doi:10.11622/smedj.2019141.
17. Langlotz CP, Allen B, Erickson BJ, Kalpathy-Cramer J, Bigelow K, Cook TS, et al. A roadmap for foundational research on artificial intelligence in medical imaging: from the 2018 NIH/RSNA/ACR/The Academy Workshop. Radiology 2019;291:781–91.
18. Liew C. The future of radiology augmented with artificial intelligence: a strategy for success. Eur J Radiol 2018;102:152–6.

Anxiety and Morale in Front-Line Healthcare Workers During the Coronavirus Disease 2019 (COVID-19) Outbreak at the National Screening Centre in Singapore

Dear Editor,

Singapore faced the threat of the novel coronavirus disease 2019 (COVID-19) when it announced her first imported case on 23 January 2020. All inbound flights from Wuhan, China have ceased that day. On 30 January 2020, the World Health Organization (WHO) declared the COVID-19 outbreak as a Public Health Emergency of International Concern.[1] The following day, Singapore recorded her first locally transmitted COVID-19 case. Within a week, on 7 February 2020, Singapore raised the "Disease Outbreak Response System Conditio" (DORSCON) level from Yellow to Orange as more new cases surfaced to suggest spread within the local community.[2] Since the escalation of the DORSCON level, attendance to Singapore's National Centre for Infectious Diseases (NCID) has been on a rise. Consequently, in addition to existing manpower from the emergency department in Tan Tock Seng Hospital, doctors from surgical specialties have been deployed to aid in the screening efforts at NCID.

We had learnt from the severe acute respiratory syndrome (SARS) outbreak in 2003 that anxiety, isolation and depression are not uncommon amongst healthcare workers (HCWs),[3] highlighting the importance of support for HCWs. Similarly, in this COVID-19 outbreak, front-line HCW face a plethora of challenges. These include isolation due to reduced interaction with families and friends for fear of transmitting disease and adjustment issues while managing illnesses that are beyond their usual job scope. Furthermore, it is not uncommon for HCWs or their colleagues to be quarantined after exposure, succumb to illness or infectious diseases. Discomfort from long hours of donning personal protective equipment (PPE) and strict infection control measures may also result in fatigue. The sudden disruption in usual work commitments, training requirements or projected leave schedules may also result in disgruntlement and significant changes in personal life plans. Besides risk exposure at work, there are practical concerns regarding disease transmission between family members living in the same household. Experiences with the public's shunning of healthcare workers and increasing difficulty in booking public transport for trips that originate and end at hospitals are just some of the examples that further burden the daily lives of HCWs. Fear-mongering by individuals and spread of falsehoods exaggerating the current COVID-19 outbreak may inevitably result in panic amongst some front-line workers as well.[4]

As the saying by Napoleon Bonaparte goes, "[i]n war, the moral is to the physical as three is to one". Similarly, in this outbreak, the morale amongst HCWs should be boosted. To date, front-line HCWs have received support in various forms. These morale boosters span from gifts of goodwill such as foods and beverages, receiving positive news coverage on their work and sacrifice, certain hospital subsidies on medical care/alternative accommodation, to the introduction of GrabCare.[5] GrabCare is a dedicated ride service developed for HCWs to travel to and from hospitals. The common message in all of these was to acknowledge and appreciate HCWs. The authors felt it would be interesting to survey the perspectives of HCWs on what has impacted their morale and to assess their anxiety levels before and after screening duties in NCID.

An anonymous online survey was conducted. The first 2 batches of front-line healthcare workers who have completed their 10-day work cycle in the NCID screening centre (between–31 January–18 February 2020) were included. Front-line HCWs included were doctors, nurses and allied health professionals. The survey consisted of 3 questions. The first question distinguished the type of profession the respondent belongs to. The second question was "What boosted your morale during the screening period?" The respondents were allowed to choose one or more options and were given a choice of "others" for further description. The third question measures the anxiety level of the respondents before and after starting working in NCID. The response options included "low, medium or high".

There were a total of 80 respondents, of which 44 were doctors, 20 were nurses and 16 were allied health professionals. They were aged between 25–35 years old. The favourite morale booster across all front-line HCWs was the donated food and drinks (53.8%) (Fig. 1). Some examples were popular comfort food like

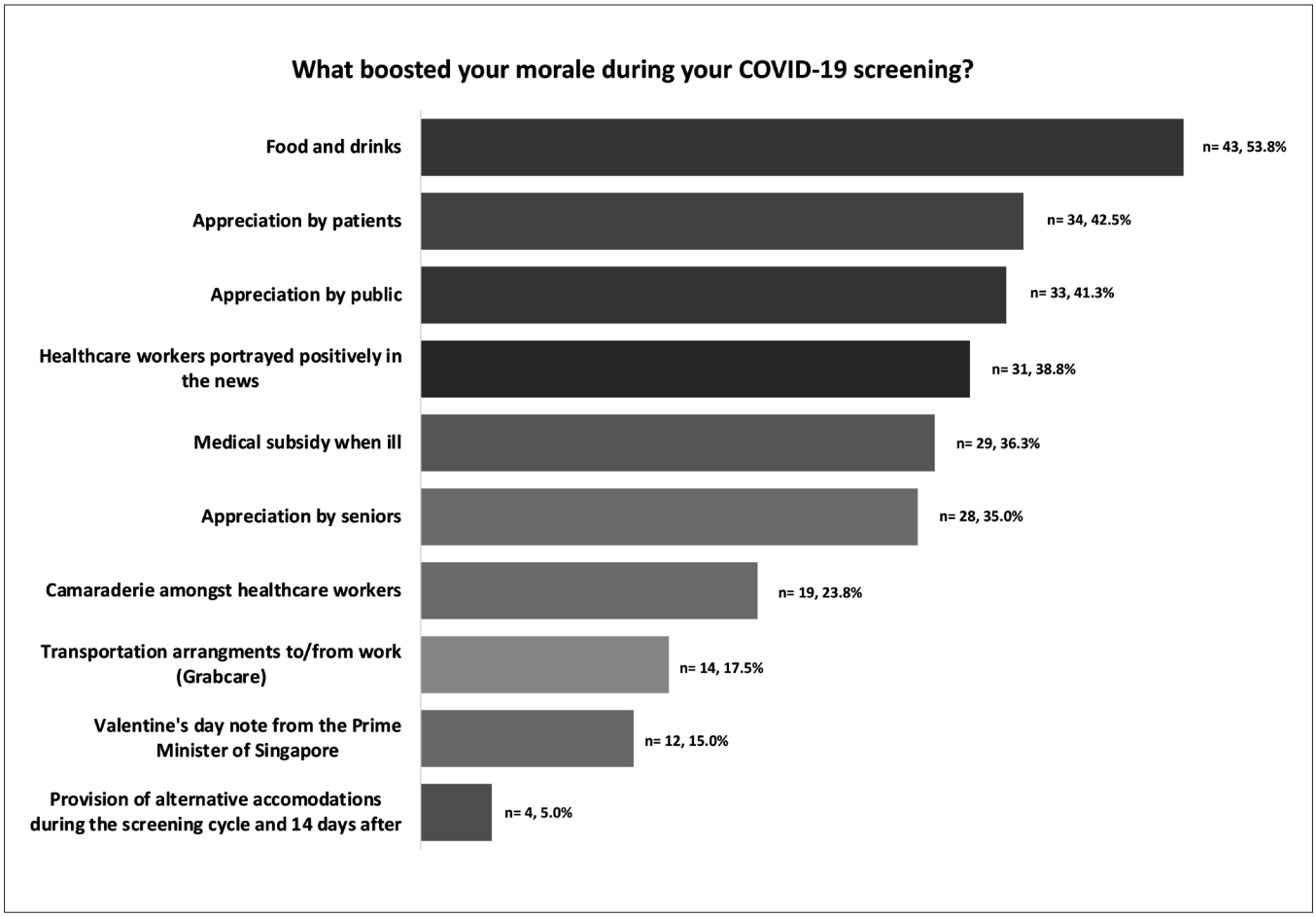

Figure 1: Morale boosters during COVID-19 screening

Old Chang Kee's curry puffs, chicken rice, sweet beverages from Gong-Cha and fresh-brewed coffee from The Coffee Bean. This is followed closely by appreciation by patients (42.5%) and the public (41.3%). In addition, more than a third were boosted by positive news on HCWs (38.8%) and presence of medical subsidies for HCWs who had fallen ill (36.3%). HCWs enjoyed the camaraderie amongst one another (23.8%), with one special mention that working alongside senior staff who volunteered to help out in the screening centre was an inspiring experience. Up to 17.5% of HCWs felt that initiatives such as GrabCare were helpful. On 14 February 2020, the Prime Minister of Singapore penned a Valentine's Day note addressed to all HCWs tackling COVID-19 to encourage and affirm HCWs during this outbreak.[6] About 15% of front-line HCWs felt that this gesture had a positive impact on their morale. Provision of alternative accommodation during the screening cycle and 14 days thereafter have encouraged 5% of HCWs. Two respondents highlighted that comfortable PPE and 1 respondent mentioned an air-conditioned environment as important factors for morale building. One other respondent enjoyed the day-offs during their screening period (i.e, the 2 day-offs that are given in every 10-day cycle).

Nurses and allied health workers (n = 22) were more likely to feel uplifted when receiving appreciation by the public as compared to doctors (n = 11), (odds ratio [OR] 10.7, I = 0.001). A higher proportion of nurses chose "Medical subsidy when they fall ill" (n = 11) as compared to doctors (n = 12), (OR 4.59, P = 0.032). On the other hand, doctors (n = 19) were more likely to be encouraged by the camaraderie they had observed and experienced as compared to nurses and allied health workers (n = 4), (OR 11.6, P = 0.0007).

Prior to commencing screening duties in NCID, all HCWs had comparable anxiety levels, P = 0.814.

After completion of screening duties in NCID, 43.1% (n = 19) of doctors reported reduction in anxiety levels while 6.8% (n = 3) reported the opposite. For allied health staff, 25% (n = 4) had increased anxiety levels whilst 43.8% (n = 7) were less anxious after screening duties. For nurses, 15% (n = 3) were less anxious but majority 60% (n = 12) reported increased anxiety levels after screening duties (Fig. 2). The changes in anxiety levels pre and post screening differed significantly amongst the three groups, P = 0.001.

Our survey, PPE found that the morale boosters were generally well appreciated as they were practical and appropriate to their needs at that point in time. Interestingly, nurses felt that being appreciated by the public was important to their morale. This is not surprising in our local context in light of repeated incidents where HCWs, especially nurses, were being shunned by the public in fear of transmission of infectious diseases.[7] On the other hand, more doctors were more likely to be encouraged by the camaraderie amongst HCWs. As the manpower for COVID-19 screening is pooled from different departments, PPE doctors were new to the job scope, environment and may not be accustomed to prolonged wear of PPE. Hence development of good working relationships between HCWs may result in a form of peer support which naturally becomes a morale booster.

(Grey: No change, : Increase, : Decrease in anxiety levels respectively)

Change in anxiety level (Doctors)		Post Screening		
		Low	Medium	High
Pre Screening	Low	13	1	1
	Medium	11	8	1
	High	5	3	1

Change in anxiety level (Nurses)		Post Screening		
		Low	Medium	High
Pre Screening	Low	1	5	1
	Medium	0	4	6
	High	0	3	0

Change in anxiety level (Allied)		Post Screening		
		Low	Medium	High
Pre Screening	Low	1	3	0
	Medium	3	3	1
	High	1	3	1

Fig. 2. Comparison of changes in anxiety level of healthcare workers before and after screening duties in the National Centre for Infectious Diseases.

Camaraderie may play a part in alleviating anxiety as well. Out of 44 doctors, 41 reported similar or reduction in anxiety levels at the completion of their 10-day cycle. Furthermore, front-line doctors received timely updates regarding new hotspots, clusters or change in screening protocols. Receiving credible up-to-date news from the institute may play a part to help doctors discern false news from social media that may unnecessarily result in panic among HCWs.

On the other hand, up to 60% of nurses reported increased anxiety levels after screening duties. A few postulated hypotheses have been suggested. Firstly, nurses were in charge of obtaining nasopharyngeal swabs for suspected cases in the screening centre. The process of the swabs tend to trigger coughing or gagging which may heighten the fear of disease transmission. Although strict infection control measures are in place during the swabbing process, the anxiety related to this process is understandable. Furthermore, nurses may not always receive first-hand or timely updates on protocol change. This may result in uncertainty and anticipation, which are components of anxiety.[8] Their level of understanding of the disease on the ground may also differ from that of doctors. On the same note, significantly more nurses than doctors were encouraged by the provision of medical subsidy if they were to fall ill. These findings suggest that the nature of morale boosters and level of support for the different types of healthcare professionals are unique. Therefore, there may be a role in tailoring strategies towards morale building based on job scopes.

Although our survey focused mainly on the practical morale boosters available during the early period of the COVID-19 outbreak in Singapore, we acknowledge the importance of other forms of morale boosters which include trust in healthcare systems, quality of leadership, perception of preparedness during the outbreak and monetary benefits etc.[9] An important factor to some would be past experiences through previous infectious disease outbreaks such as SARS in 2003 and the H1N1, swine-flu pandemic in 2011. Although our study included HCWs who have never been involved in any of the infectious disease outbreaks in the past, news on the nation's efforts in health innovation, advances in epidemiology and improved preparedness since

2003 may instil confidence in these HCWs. Lastly, front-line HCWs extend beyond those included in our survey. There is a large group of HCWs who play a critical role in managing patients in outpatient services who are likely to benefit from good morale during this outbreak as well.

Each and every infectious disease outbreak draws a unique healthcare response. The morale of front-line HCWs inevitably reflects the culture and effectiveness of the health care system. Understanding the factors that affect their morale can help improve and tailor the support provided by the public, institutions and the government. The authors hope that this article will inspire more healthcare systems to adopt measures to enhance the morale of their HCWs during this outbreak.

REFERENCES

1. World Health Organization Regional Office for Europe. Coronavirus disease (COVID-19) outbreak. Available at: http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19. Accessed on 22 February 2020.
2. Ministry of Health Singapore. Updates on COVID-19 (Coronavirus Disease 2019) Local Situation. Available at: https://www.moh.gov.sg/covid-19. Accessed on 22 February 2020.
3. Maunder R. The experience of the 2003 SARS outbreak as a traumatic stress among frontline healthcare workers in Toronto: lessons learned. Philos Trans R Soc Lond B Biol Sci 2004;359:1117–25.
4. Tham Y. MOH uses fake news law to counter falsehoods. The Straits Times, 15 February 2020. Available at: https://www.straitstimes.com/politics/moh-uses-fake-news-law-to-counter-falsehoods. Accessed on 22 February 2020.
5. Grab Singapore. Grab to pilot GrabCare transport service for frontline healthcare workers. Available at: https://www.grab.com/sg/press/others/grab-to-pilot-grabcare-transport-service-for-frontline-healthcare-workers. Accessed on 22 February 2020.
6. Lai L. PM Lee pens Valentine's Day note to healthcare workers at front line of coronavirus. The Straits Times, 14 February 2020. Available at: https://www.straitstimes.com/singapore/pm-lee-pens-valentines-day-note-to-healthcare-workers-at-front-line-of-coronavirus. Accessed on 22 February 2020.
7. Tan A. Support healthcare workers, don't shun them: Gan Kim Yong. The New Paper, 13 February 2020. Available at: https://www.tnp.sg/news/singapore/support-healthcare-workers-not-shun-them-gan-kim-yong. Accessed on 22 February 2020.
8. Grupe DW, Nitschke JB. Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. Nat Rev Neurosci 2013;14:488–501.
9. Lim GH, Lim BL, Vasu A. Survey of factors affecting health care workers' perception towards institutional and individual disaster preparedness. Prehosp Disaster Med 2013;28:353–8.

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Decision-Making in Dementia Care: a Qualitative Study of Chinese Family Caregivers in Singapore

Dear Editor,

In 2003, the prevalence of dementia in individuals aged ≥60 years old in Singapore was 5.2%;[1] in a recent epidemiological study, it had risen to 10%.[2] As the population ages, an increasing number of people will be caring for their loved ones with dementia. In many Asian countries, family caregivers are intimately involved in the care of older adults. In Singapore, family caregivers struggled with their caregiving responsibilities and there is a high prevalence of depressive symptoms among them.[3,4] It has been found that problematic family environment and lower levels of decision-making satisfaction can have a cumulative effect on caregiver depression.[5] Decision-making satisfaction was described as how happy family members were with regards to the discussion related to care planning.[5] The proposed Path Model from a general stress paradigm posited that caregiving context and family environment might have an indirect effect on depression through decision-making satisfaction.[5] The decision-making process is suggested to have the potential to engender additional strain on family caregivers.[5]

A recent local study suggested that most individuals with early cognitive impairment declined any discussion on advanced care planning (ACP).[6] Decisions on care delivery are often made by family caregivers on behalf of persons with dementia (PWD) who lacked the mental capacity to do so. In elderly individuals with cancer or organ failure, factors such as an understanding of their prognoses and ACP have been shown to influence their acceptance of palliative care services and quality of life.[7,8] In PWD, cognitive decline poses specific challenges in their understanding of prognosis and ACP. Consequently, family members often report major barriers and psychological distress in making care decisions.[9]

To date, most studies on dementia caregiver interventions in non-Western populations had emphasised behavioural interventions and their impact on the quality of life of caregivers.[10] There is a dearth of literature on how decision-making roles in dementia caregivers impact their well-being and caregiving role. To the best of our knowledge, this was the first qualitative study of decision-making among family caregivers of PWD in Singapore. With an understanding of these challenges, appropriate support can be rendered to family caregivers and PWD in making care decisions.

Materials and Methods

Patients who were referred to the memory clinics in our organisation with a diagnosis of dementia and had a family caregiver were screened. Informed consent was obtained and a questionnaire was used to collect their sociodemographic data. Information on diagnosis and severity of dementia was determined from clinical notes. The study was approved by the Centralised Institutional Review Board (CIRB 2013/583/A).

Interviews with caregivers were conducted by the Principal Investigator (PI) and were guided by questions on diagnosis, treatment and care decisions (Fig. 1). Each interview was digitally recorded and transcribed verbatim. Thematic analysis was used to identify themes in decision-making.

The initial themes were summarised by the PI and the data was coded and analysed using Atlas.ti, version 8.0 (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany). Data collection ceased after no new themes were found. A total of 14 participants were included in the study.

Results

The clinical variables and sociodemographics of 14 PWD and their caregivers are summarised in Table 1. All the participants were Chinese in ethnicity. Almost all PWD were women and most of them had moderate to severe dementia. Most caregivers agreed with the diagnosis of dementia; however, only 3 of them endorsed dementia as a terminal illness. The qualitative analysis identified 4 primary themes that are described in the following sections.

Decision to Reveal Diagnosis of Dementia

Nine caregivers wished their loved ones to be informed of the diagnosis of dementia. Family members felt that they should be open with them because they had the right to know and would cooperate better with treatment after they were informed of their diagnosis.

The diagnosis

1. Does your loved one have a memory problem?
2. Does your loved one have "dementia"?
3. What else would you like to know?
4. When would you like to know?
5. How do you wish to find out?
6. Is your loved one in the mild, moderate or severe stage of dementia?
7. Does s/he have a terminal illness?

Information about dementia

8. Do you wish your loved one to be informed of the diagnosis of dementia? Why?
9. How should it be communicated?
10. What is important to mention?
11. Who should tell the patient?

Care and treatment options

12. What care and treatment options are there?
13. How do you find out about them?
14. Why would you consider these options?

Making the decision

15. What is your greatest fear/concern with regards to the care of your loved one?
16. What are other decisions you will have to discuss with your loved one?
17. If you have not done so, why?
18. When would you discuss with your loved one? Why?
19. Who should be the one to discuss with your loved one? Why?
20. In the event of poor feeding, would you consider tube feeding? Why?
21. If s/he needs to be restrained to ensure safety, would you be agreeable? Why?
22. Does your loved one have a living will? If yes, who made the decision for the living will? Why do you think it is important? If not, do you intend to help your loved one do so? Why?
23. Would you be comfortable to discuss funeral arrangements with your loved one before s/he becomes too forgetful? Why?
24. What are your views about hospital admission for your loved one with dementia?
25. What would help you make your choices easier?

Fig. 1. Interview guide. The questions served as a guide to gather information on diagnosis, information about dementia, care and treatment options and care decisions that family caregivers must make currently and in future. The guide was designed to understand the experiences of family caregivers and to identify difficult decisions that were made by them, and the enablers and barriers to the decision-making process.

In the words of caregiver 7, "At least get her mentally prepared. At least she can face, we don't need to hide from her. So she can actually accept the facts … so she will accept. At least prepare and accept the facts that there will be some difficulty in handling her living style here and there."

Caregivers of PWD 2, 4, 6 and 13 chose not to disclose the diagnosis (their sociodemographic data are summarised in Table 1). They feared that PWD would not be able to accept the bad news and this could worsen the situation.

Challenges in Making Care Decisions

About half of caregivers would not discuss future care decisions. There was a general perception that PWD would trust them to make decisions on their behalf. A total of 3 secondary themes were identified: 1) difficulties in understanding the life-limiting nature of dementia, 2) perceived refusal of PWD to cooperate with treatment and 3) helplessness of caregivers with regards to caregiving.

According to caregiver 3, "Maybe because her type of dementia she's the mild type in the sense she's not the aggressive type so it's easier to handle ... And that she must really accept what we say. When we tell her you have not bathed, she kept on insisting she had bathed … She has to accept certain things she can't remember actually."

Decisions to Be Made in Caring for PWD

The common decisions that were highlighted involved finances, freedom to leave home and admission to a nursing home or dementia day care centre. Difficult decisions were identified as those that related to care in the final phase of dementia, namely nasogastric tube feeding, physical restraints, hospital admission and funeral arrangements.

Caregivers also expressed their preference to let nature takes its course. They were unfamiliar with options such as lasting power of attorney (LPA) and ACP, and would prefer to follow the recommendations of the physicians. Caregiver 7 described it as "Until that stage, then we can decide."

Support for Family Caregivers to Care for PWD

Two areas were repeatedly highlighted by the participants: practical care of their loved ones with dementia and more support in understanding the care needs of PWD.

In the words of caregiver 12, "Actually at the beginning, as soon as she is diagnosed with dementia, it's good to have a relatively good understanding of the condition as well as the kind of care giving that is necessary. And the kind of help that can be given to the caregiver ... yah, so I guess it's informing us with that compassion as well not just something that is very clinical. So I guess that helps

Table 1. Sociodemographic Data and Clinical Characteristics of PWD and Their Caregivers

Number	PWD								Caregiver			
	Dementia Type	Dementia Severity (MMSE Score)	Age (Years)	Gender	Marital Status	Number of Children	Education	Religion	Relationship	Age (Years)	Marital Status	Education
1	Mixed	Mild (21)	84	Male	Married	3	Secondary	Taoism	Daughter	57	Single	Tertiary
2	AD	Moderate (19)	89	Female	Divorced	4	Tertiary	Buddhism	Daughter	55	Married	Secondary
3	Mixed	Moderate (13)	84	Female	Widowed	2	Secondary	Christianity	Son	59	Widowed	Tertiary
4	Mixed	Moderate (17)	79	Female	Divorced	4	Primary	Buddhism	Son	58	Married	Secondary
5	AD	Mild (23)	67	Female	Single	0	Primary	Taoism	Sister	59	Married	Secondary
6	Mixed	Moderate (10)	78	Female	Widowed	4	Nil	Christianity	Son	50	Married	Tertiary
7	Mixed	Severe (5)	78	Female	Widowed	6	Nil	Buddhism	Son	47	Married	Tertiary
8	Mixed	Moderate (16)	77	Female	Married	2	Primary	Nil	Son	49	Married	Tertiary
9	AD	Moderate (11)	87	Female	Widowed	7	Nil	Nil	Son	59	Married	Secondary
10	Mixed	Moderate (13)	85	Female	Widowed	5	Nil	Taoism	Son	49	Married	Secondary
11	Mixed	Moderate (17)	81	Female	Married	1	Nil	Nil	Daughter	42	Single	Secondary
12	Mixed	Moderate (13)	85	Female	Widowed	5	Nil	Christianity	Daughter	48	Married	Tertiary
13	AD	Mild (20)	82	Female	Married	2	Secondary	Christianity	Spouse	80	Married	Tertiary
14	AD	Severe (0)	66	Female	Married	2	Secondary	Christianity	Spouse	66	Married	Secondary

AD: Alzheimer's disease; MMSE: Mini-Mental State Examination; PWD: Persons with dementia

because you will be at a point of time where it's just so emotionally difficult … ."

Discussion

To the best of our knowledge, this is the first local qualitative study that investigated the decision-making process amongst Chinese family caregivers of PWD. As dementia progresses, medical practitioners often rely on family members to understand and choose treatments with assumed accuracy. In our study, most family caregivers supported the decision to discuss the diagnosis of dementia with patients, but half of them chose not to discuss future care plans and decisions. A common theme that emerged in our study was the belief of caregivers that their loved ones with dementia would entrust them with this role. The value of familism—needs of the family are perceived as more important than those of individual members—is an entrenched belief in Asia.[11–3] The need to maintain family harmony and the influence of Confucianist and Taoist ideas that family members would be entrusted with the care of their ailing elders[14] might be possible reasons to explain this trend that was observed in our study.

Findings in the literature on decision-making and family caregiving of elderly loved ones in non-Asian settings suggested that families tended to rely on family members—rather than professionals—in making elder care decisions.[15-6] A previous study had shown that elderly Singaporeans were reluctant to engage in discussions on end-of-life (EOL) care and preferred their physicians to take on the role of surrogate decision-maker on their behalf.[17] Similarly, in our study, family caregivers preferred their doctors to help them with making critical decisions in the last stage of dementia.

In the elderly, the take-up rate for discussions on ACP was previously noted to be modest at 38%.[6] It would not be a surprising finding that family caregivers in our study had encountered difficulties in discussing care decisions with PWD. Previous studies also showed that the lower take-up rate for ACP was associated with more advanced cognitive impairment.[6,8] Consequently, it would be pertinent to encourage and engage family caregivers to initiate ACP with their loved ones who were diagnosed with early-stage dementia.

Another common theme was that family caregivers preferred to deal with the challenges of care when they surface later. Half of our participants believed that their loved ones with dementia would trust them to make decisions on their behalf. However, family members were not familiar with ACP and LPA, and would defer critical decision-making to their doctors. In the United Kingdom, a study had shown that both PWD and their caregivers showed marked uncertainty about ACP and EOL treatment preferences even when the caregiving relationship was perceived to be good.[18]

In our study, the concept of dementia as a terminal illness was not easily accepted by family caregivers. Consequently, they did not see the necessity to engage PWD in timely discussions when the latter still retained their decision-making capacity. Other studies had also highlighted that both professional[17] and family caregivers[19] did not view dementia as a terminal illness. This might have contributed to neglect in discussing EOL care for PWD and their care providers.[18,20] In our study, the common difficult decisions were identified as those that related to EOL care, namely nasogastric tube feeding, physical restraints and hospital admissions.

The lack of understanding of dementia as a terminal illness is an issue that must be addressed in a sensitive manner. A secondary theme that was found in our study was the feeling of helplessness experienced by family caregivers in their caregiving role. At the same time, they also yearned for more support to understand the care needs of their loved ones. Consequently, family members would benefit from early and continued practical and psychological support in their journey towards EOL care in the dementing process.

A limitation of this study was that it recruited family members whose loved ones had moderate to severe dementia and caregivers were mainly children of PWD. Consequently, the results on the challenges in decision-making might not be generalised to other familial caregiving relationships. As we had difficulty recruiting non-Chinese family members into the study, the results might also not be relevant to other ethnic groups in Singapore.

Conclusion

Besides their feeling of helplessness and uncertainty in making treatment decisions on behalf of PWD, family caregivers tended to rely on medical practitioners to make difficult EOL care decisions. They also lack understanding of dementia as a terminal illness[179,19] and expressed marked uncertainty about ACP.[18] Discussions about difficult decisions were also not perceived as urgent or necessary. Efforts should be made to raise awareness that dementia is a life-limiting illness and to facilitate discussions of ACP in a sensitive manner. With findings of low take-up rate for ACP that followed a decline in cognitive function in Western populations,[6,7] discussions with PWD and their family caregivers on ACP during the early stage of dementia—with the involvement of medical practitioners—could help them to make informed decisions on future care that include ACP and EOL care.

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REFERENCES

1. Chiam PC, Ng TP, Tan LL, Ong PS, Ang A, Kua EH. Prevalence of dementia in Singapore—results of the National Mental Health Survey of the Elderly 2003. Ann Acad Med Singapore 2004;33:S14–5.
2. Subramaniam M, Chong SA, Vaingankar JA, Abdin E, Chua BY, Chua HC, et al. Prevalence of dementia in people aged 60 years and above: results from the WiSE study. J Alzheimers Dis 2015; 45:1127–38.
3. Malhotra C, Malhotra R, Østbye T, Matchar D, Chan A. Depressive symptoms among informal caregivers of older adults: insights from the Singapore Survey on Informal Caregiving. Int Psychogeriatr 2012;24:1335–46.
4. Ying J, Yap P, Gandhi M, Liew TM. Validity and utility of the Center for Epidemiological Studies Depression Scale for detecting depression in family caregivers of persons with dementia. Dement Geriatr Cogn Disord 2019;47:323–34.
5. Deimling GT, Smerglia VL, Schaefer ML. The impact of family environment and decision-making satisfaction on caregiver depression: a path analytic model. J Aging Health 2001;13:47–71.
6. Cheong K, Fisher P, Goh J, Ng L, Koh HM, Yap P. Advance care planning in people with early cognitive impairment. BMJ Support Palliat Care 2015;5:63–9.
7. Robinson L, Dickinson C, Rousseau N, Beyer F, Clark A, Hughes J, et al. A systematic review of the effectiveness of advance care planning interventions for people with cognitive impairment and dementia. Age Ageing 2012;41:263–9.
8. Dening KH, Jones L, Sampson EL. Advance care planning for people with dementia: a review. Int Psychogeriatr 2011;23:1535–51.
9. Carter G, McLaughlin D, Kernohan WG, Hudson P, Clarke M, Froggatt K, et al. The experiences and preparedness of family carers for best interest decision-making of a relative living with advanced dementia: a qualitative study. J Adv Nurs 2018;74:1595–604.
10. Wu B, Petrovsky DV, Wang J, Xu H, Zhu Z, McConnell ES, et al. Dementia caregiver interventions in Chinese people: a systematic review. J Adv Nurs 2019;75:528–42.
11. Tuomola J, Soon J, Fisher P, Yap P. Lived experience of caregivers of persons with dementia and the impact on their sense of self: a qualitative study in Singapore. J Cross Cult Gerontol 2016;31:157–72.
12. Chee YK, Levkoff SE. Culture and dementia: accounts by family caregivers and health professionals for dementia-affected elders in South Korea. J Cross Cult Gerontol 2001;16:111–25.
13. Coulton CJ, Dunkle RE, Goode RA, Mackintosh J. Discharge planning and decision making. Health Soc Work 1982;7:253–61.
14. Chan SWC. Family caregiving in dementia: the Asian perspective of a global problem. Dement Geriatr Cogn Disord 2010;30:469–78.
15. Keith PM. Patterns of assistance among parents and the childless in very old age: implications for practice. J Gerontol Soc Work 1983;6:49–59.
16. Smerglia VL, Deimling GT, Barresi CM. Black/White family comparisons in helping and decision-making networks of impaired elderly. Family Relations 1988;37:305–9.
17. Low JA, Ng WC, Yap KB, Chan KM. End-of-life issues—preferences and choices of a group of elderly Chinese subjects attending a day care centre in Singapore. Ann Acad Med Singapore 2000;29:50–6.
18. Dening KH, King M, Jones L, Vickerstaff V, Sampson EL. Advance care planning in dementia: do family carers know the treatment preferences of people with early dementia? PloS One 2016; 11:e0159056.
19. McCarthy M, Addington-Hall J, Altmann D. The experience of dying with dementia: a retrospective study. Int J Geriatr Psychiatry 1997;12:404–9.
20. Sampson EL, Gould V, Lee D, Blanchard MR. Differences in care received by patients with and without dementia who died during acute hospital admission: a retrospective case note study. Age Ageing 2006;35:187–9.

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Indurated Skin and Iron Overload—the Missing Link

A 62-year-old Chinese woman with a history of haemochromatosis and secondary hemosiderosis presented with gradual onset of skin hardening and increased prominence of hair follicles on bilateral forearms and back of the neck for 9 months. There was no pain or itch in the affected areas. Systemic review did not show Raynaud's phenomenon, dysphagia, dyspepsia, sicca symptoms or joint pain.

Physical examination revealed sclerodermoid, indurated plaques on forearms and arms with speckled hypo- and hyperpigmentation. Erosions were seen on the dorsum of hand and forearm (Fig. 1). On the nape, speckled hypo- and hyperpigmentation was also seen with a sharp cut-off at the collar line (Fig. 2). Skin biopsy demonstrated thickened collagen bundles in the dermis (Fig. 3). Skin induration improved with hydroxychloroquine 100 mg twice a week.

What is the most likely diagnosis?

A. Chronic actinic dermatitis (CAD)
B. Eosinophilic fasciitis
C. Porphyria cutanea tarda (PCT)
D. Scleroderma
E. Scleromyxedema

Discussion

Although the distribution (on the face and appearance of a "V" shape on the neck and forearms) fits the diagnosis of CAD (sun-exposed areas), the morphology of CAD is chronic, lichenified and eczematous plaques. Also, eosinophilic fasciitis usually presents with induration of the limbs with shallow grooves or furrows in the skin that run along the paths of underlying veins, and is usually associated with pain and swelling and inflammation of the skin.

Scleroderma has an initial oedematous phase (pitting oedema of digits) with subsequent sclerosis. It is often accompanied by Raynaud's phenomenon with synovitis and systemic involvement (cardiac, renal, gastrointestinal and pulmonary).[1] Scleromyxedema usually presents as waxy papules in a linear array. The surrounding skin is shiny and indurated, and is sclerodermoid in appearance. Typically, it affects the hands, forearms, head, neck, upper trunk and thighs.[2]

In our patient, findings of quantitative assay of blood and urine samples showed raised total urinary and erythrocyte porphyrins. Together with her clinical

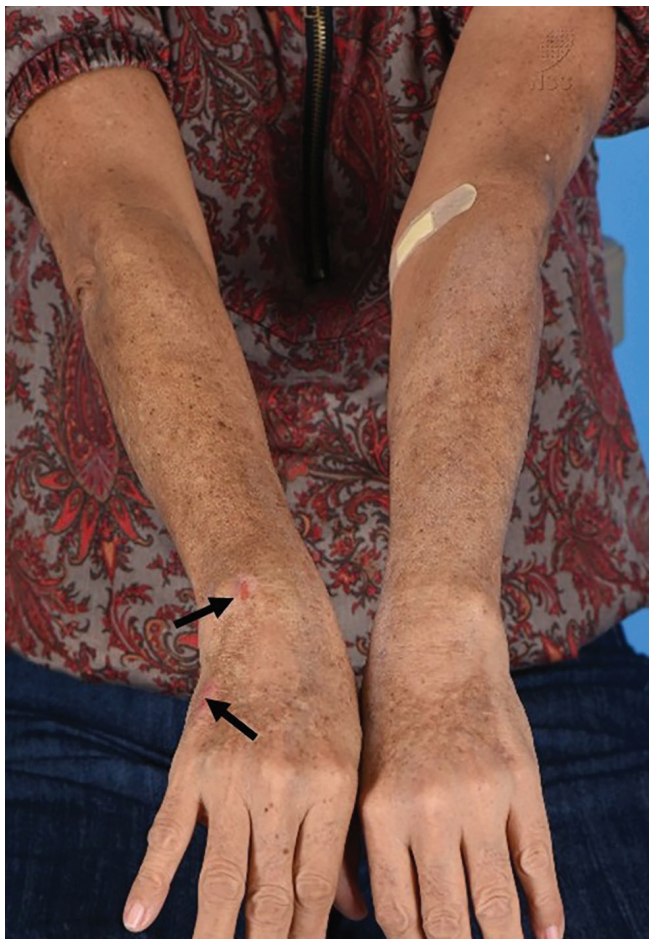

Fig. 1. Indurated plaques on forearms and arms with speckled hypo- and hyperpigmentation and erosions (black arrows).

Correct answer: C

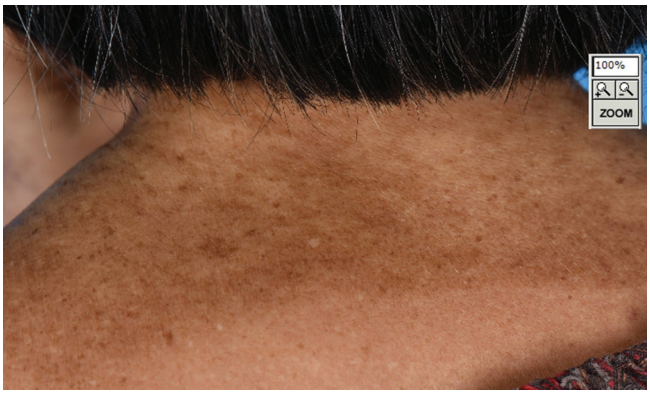

Fig. 2. Indurated plaques with speckled hypo- and hyperpigmentation with a sharp cut-off at the collar line.

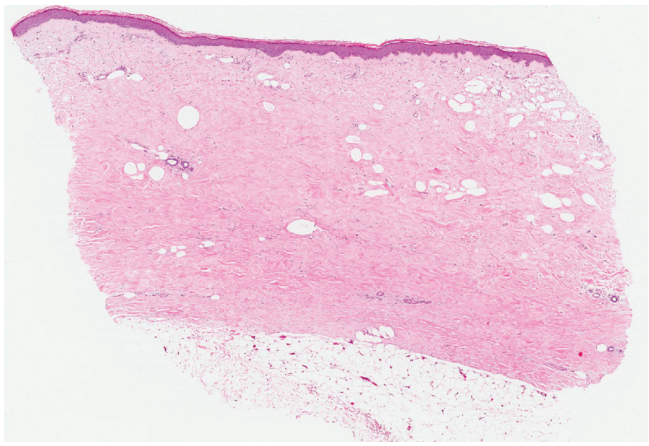

Fig. 3. Dermis shows widespread thickened collagen bundles. Fusion of adjacent collagen bundles and loss of intercollagenous cleft spaces are seen in some areas. The eccrine glands are compressed and appear high-lying due to collagen that is laid down below which extends to the dermosubcutaneous junction with a flat edge (hematoxylin and eosin stain, magnification × 40).

presentation, the results confirmed the diagnosis of PCT. PCT is the most common form of porphyria seen in dermatological practice and its clinical features include sclerodermoid plaques, erosions, vesicles and hyperpigmentation in sun-exposed areas. It is also associated with hypertrichosis.[3]

PCT is characterised by reduced activity of uroporphyrinogen decarboxylase (UROD) enzyme, which could be attributed to inherited genetic defects or acquired factors that caused inactivation of the normal enzyme. There are 3 types of PCT. Type 1 (sporadic) is the most common form and accounts for 80% of cases and occurs in the absence of UROD gene mutation. Type 2 (familial) is characterised by a UROD mutation that affects 1 allele. Type 3 (familial) is also characterised by familial inheritance, but UROD mutation is absent and it may be attributed to other hereditary factors such as haemochromatosis gene mutation.[4]

In all 3 types of PCT, hepatic UROD activity is decreased and leads to accumulation of porphyrins in the liver. Porphyrins are then transported from the liver to the skin, where they absorb sunlight and enter an excited state (photoactivation). This abnormal activation results in characteristic damage to the skin (blister formation and skin hardening from dermal fibrosis).

Several factors can predispose individuals to become more susceptible to the development of PCT. They include alcohol use, smoking, hepatitis C, human immunodeficiency virus and oestrogen supplementation.[5] However, the most important factor is iron overload that occurs in conditions such as haemochromatosis.[6,7] Increased hepatic iron facilitates the formation of oxygen free radicals that contribute to oxidative formation of a UROD inhibitor.

Full blood count is usually normal while serum aminotransferase levels are elevated. Urine test will yield a pink fluorescence when it is illuminated under Wood's light. In PCT, urine porphyrin excretion is increased. The excreted porphyrins are predominantly uroporphyrin and heptacarboxyl porphyrin. Quantitative assay of porphyrins can be performed in specialised centres.[8]

All patients with PCT who have active skin lesions should receive primary therapy including phlebotomy or low-dose hydroxychloroquine. In a prospective pilot study that involved 48 consecutive patients with PCT, time required to normalise plasma porphyrin levels—a predictor of clinical improvement—was similar for both treatments.[9]

REFERENCES

1. Wong JS, Ng SC. Imaging of thoracic manifestations of scleroderma. Ann Acad Med Singapore 1998;27:76–82.
2. Lim VZ, Tey HL. Diffuse indurated skin. Ann Acad Med Singapore 2016;45:379–80.
3. Mascaro JM. The porphyrias: a brief overview based on 25 years of experience (1969–1994) by the Department of Dermatology of the Hospital Clinic and Faculty of Medicine of Barcelona, Spain. J Dermatol 1995;22:823–8.
4. Jalil S, Grady JJ, Lee C, Anderson KE. Associations among behavior-related susceptibility factors in porphyria cutanea tarda. Clin Gastroenterol Hepatol 2010;8:297–302.

5. Bonkovsky HL, Poh-Fitzpatrick M, Pimstone N, Obando J, Di Bisceglie A, Tattrie C, et al. Porphyria cutanea tarda, hepatitis C, and HFE gene mutations in North America. Hepatology 1998;27:1661–9.
6. Mehrany K, Drage LA, Brandhagen DJ, Pittelkow MR. Association of porphyria cutanea tarda with hereditary hemochromatosis. J Am Acad Dermatol 2004;51:205–11.
7. Bovenschen HJ, Vissers WHPM. Primary hemochromatosis presented by porphyria cutanea tarda: a case report. Cases J 2009;2:7246.
8. Deacon AC, Elder GH. ACP Best Practice No 165: front line tests for the investigation of suspected porphyria. J Clin Pathol 2001;54:500–7.
9. Singal AK, Kormos-Hallberg C, Lee C, Sadagoparamanujam VM, Grady JJ, Freeman Jr DH, et al. Low-dose hydroxychloroquine is as effective as phlebotomy in treatment of patients with porphyria cutanea tarda. Clin Gastroenterol Hepatol 2012;10:1402–9.

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"We're all in this human experience together, so let's try to be kind, gracious, and compassionate to each other."

Kailin Gow
American author

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