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My Health Record: a community pharmacy perspective

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Digital healthcare records aim to facilitate the delivery of safe, efficient and effective health care while connecting different points of the healthcare system so that information can be shared securely. These records can impact on almost every aspect of healthcare delivery. This includes how healthcare professionals and patients interact with each other, how health information is stored and used, and how patients manage their own health through electronic apps and devices. Due to the rapid evolution of digital health care, today's health professionals, including pharmacists, need an understanding of the expectations, opportunities and challenges that digital health technologies present.

The My Health Record system is one of the first initiatives in the world aimed at delivering an electronic, personally controlled health record for the entire population of a country. The Australian Government determined that by the end of 2018 every Australian would have a My Health Record unless they chose not to.

One of the key potential benefits of a national electronic health record will be a reduction in the risk of medication misadventure (adverse drug events and medication errors), which results in more than 230,000 Australians being admitted to hospital each year. These hospitalisations cost the healthcare system at least \$1.2 billion annually.¹ However, this represents the tip of the iceberg because this figure does not include general practice or specialist visits, the cost of investigations, or presentations to community pharmacy.

Pharmacists already store information such as drug-dispensing histories that may not be available to other healthcare professionals, including the patient's GP. By making this information securely available through My Health Record to other healthcare providers, pharmacists can contribute to a comprehensive overview of the patient's medicine use, including medication adherence and persistence inferred by the frequency of dispensing. This may improve healthcare outcomes. In particular, access to dispensing records and other drug-related histories can facilitate effective and efficient medicines reconciliation at transitions of care, such as admission to and discharge from hospital. An Australian study found that two-thirds of initial hospital medication charts contain at least one error, and access

to community pharmacy dispensing records reduces the time taken to identify and correct these errors.²

Most pharmacists and authorised pharmacy staff will interact with the My Health Record system at the point of dispensing through the use of compliant dispensing software. The provision of comprehensive dispensing information to My Health Record will give a more complete picture of the patient's medicines, as well as an insight into the way they are taken, particularly if the pharmacist supplements the record of prescribed drugs by recording over-the-counter and complementary medicines. This information may be valuable to the patient's GP, specialists, hospital clinicians, the patient and their carer.³

Historically, community pharmacists have not had ready access to verifiable clinical information about the patient's medical conditions, pathology or imaging results, or the indication for the prescribed medicine, to help inform their clinical decision making. This clinical information will give the pharmacist a greater opportunity to improve the use of medicines in the Australian community and usefully contribute to reducing medication misadventure, particularly at transitions of care. However, there will be challenges imposed by factors such as compatibility with pharmacy workflow and the need for adequate clinical knowledge and skills to leverage information in electronic health records to improve the quality use of medicines and patient outcomes.^{4,5}

The system architecture of My Health Record allows pharmacists to contribute dispensing records and event summaries. With advances in the usability of pharmacy computer systems and professional service recording platforms, event summaries could in the future describe a consultation with a pharmacist about a minor ailment, a MedsCheck Service or a Home Medicines Review. This will ensure that services delivered by a pharmacist in a community pharmacy can be added (with patient consent) to My Health Record, and then be viewed by other health professionals so reducing the risk of fragmentation of care. Advances in secure message delivery can also ensure that details of these consultations can be provided to other healthcare providers when the patient deems it appropriate. Health information exchange systems, such as My Health Record, can facilitate the integration of

pharmacists into care teams to improve the use of medicines and patient outcomes.⁶ Systems enabling communication and the sharing of health information should facilitate good working relationships between health professionals, and enable collaborative patient-centred care.⁷ In Kansas, community pharmacists were able to use a state health information exchange to collect hospital discharge information from patients' electronic medical records to facilitate medication reviews and the identification of drug therapy problems following discharge. As a result, there was a statistically significant reduction in hospital readmissions.⁸ However, there is currently a paucity

of published information describing the outcomes of the integration of shared electronic health records in community pharmacies. Further research is needed.^{9,10}

Having pharmacy information available to prescribers and clinical information available to pharmacists will provide all professions with an opportunity to enhance the continuum of the quality use of medicines in Australia. A comprehensive post-implementation evaluation should be performed to assess whether this potential is fulfilled. ◀

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REFERENCES

1. Roughead L, Semple S, Rosenfeld E. Literature review: medication safety in Australia. Australian Commission on Safety and Quality in Health Care: Sydney; 2013. <https://www.safetyandquality.gov.au/publications/literature-review-medication-safety-in-australia> [cited 2019 Mar 1]
2. Tompson AJ, Peterson GM, Jackson SL, Hughes JD, Raymond K. Utilizing community pharmacy dispensing records to disclose errors in hospital admission drug charts. *Int J Clin Pharmacol Ther* 2012;50:639-46. <https://doi.org/10.5414/CP201720>
3. Wright DJ, Twigg MJ. Community pharmacy: an untapped patient data resource. *Integr Pharm Res Pract* 2016;5:19-25. <https://dx.doi.org/10.2147/FIPRP.S83261>
4. Nelson SD, Poikonen J, Reese T, El Halta D, Weir C. The pharmacist and the EHR. *J Am Med Inform Assoc* 2017;24:193-7. <https://doi.org/10.1093/jamia/ocw044>
5. Hughes CA, Guirguis LM, Wong T, Ng K, Ing L, Fisher K. Influence of pharmacy practice on community pharmacists' integration of medication and lab value information from electronic health records. *J Am Pharm Assoc* 2011;51:591-8. <https://doi.org/10.1331/JAPhA.2011.10085>
6. Pellegrin K, Chan F, Pagoria N, Jolson-Oakes S, Uyeno R, Levin A. A statewide medication management system: health information exchange to support drug therapy optimization by pharmacists across the continuum of care. *Appl Clin Inform* 2018;9:1-10. <https://doi.org/10.1055/s-0037-1620262>
7. Keller ME, Kelling SE, Cornelius DC, Oni HA, Bright DR. Enhancing practice efficiency and patient care by sharing electronic health records. *Perspect Health Inf Manag* 2015;12:1b.
8. Fanizza FA, Ruisinger JF, Prohaska ES, Melton BL. Integrating a health information exchange into a community pharmacy transitions of care service. *J Am Pharm Assoc* 2018;58:442-9. <https://doi.org/10.1016/j.japh.2018.02.012>
9. Bacci JL, Berenbrok LA. Innovative advances in connectivity and community pharmacist patient care services: implications for patient safety. *Pharmacotherapy* 2018;38:867-74. <https://doi.org/10.1002/phar.2148>
10. Hohmeier KC, Spivey CA, Boldin S, Moore TB, Chisholm-Burns M. Implementation of a health information exchange into community pharmacy workflow. *J Am Pharm Assoc* 2017;57:608-15. <https://doi.org/10.1016/j.japh.2017.05.009>

FURTHER READING

Pearce R, Whyte I. Electronic medication management: is it a silver bullet? *Aust Prescr* 2018;41:32-3. <https://doi.org/10.18773/austprescr.2018.012>

Wheeler AJ, Scahill S, Hopcroft D, Stapleton H. Reducing medication errors at transitions of care is everyone's business. *Aust Prescr* 2018;41:73-7. <https://doi.org/10.18773/austprescr.2018.021>

Real-time prescription monitoring: lessons from Tasmania

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Real-time prescription monitoring programs are effective in improving clinical decision-making. They also reduce doctor shopping and the diversion of controlled substances.¹ These programs therefore have the potential to reduce harm from prescription drugs including deaths from opioid poisoning. Coroners, and pharmacy and medical representative groups have been calling for real-time prescription monitoring for many years.

In 2009, Tasmania was the first state to implement a real-time prescription monitoring system called DORA (Drugs and Poisons Information System Online Remote Access). Initially, DORA only provided information to Tasmanian Department of Health regulators but had plans to implement access for clinicians as a priority. From 2011, DORA enabled clinicians to view clinical information and dispensing data about Schedule 8 drugs, and current and past authorities issued for the prescribing of Schedule 8 drugs to specific patients. It can confirm whether or not the patient has been declared drug-dependent or a drug seeker (as defined by the Tasmanian *Poisons Act 1971*) and if the patient has ever been treated in Tasmania for an opioid substance use disorder. Currently the use of DORA by clinicians is not mandatory, however this is a requirement of many US systems and could become mandatory in some Australian jurisdictions.

Victoria started a trial of its monitoring in 2018, and other jurisdictions such as Western Australia and the Australian Capital Territory are expected to follow. The Australian Government is supporting states and territories to adopt real-time prescription monitoring as soon as possible. It has been actively facilitating the development of policies and software solutions to enable access to patient-specific information across state and territory borders.

Victorian Coroners' data suggest approximately 85% of deaths from pharmaceutical poisoning are from medicines legally prescribed and dispensed to the deceased. Very few deaths are due to diverted prescribed medicines. Only about 25% of all deaths from prescription medicine poisoning involved multiple prescribers.²

Between 2012 and 2016, 3993 Australians died from prescription opioid poisoning. These figures represent an increase of approximately 113% compared

with 2002–06 (1877 opioid poisoning deaths). Tasmania's per capita death rate from prescription opioids was approximately 30% above the national average between 2002 and 2006 and changed to approximately 27% below the national average between 2012 and 2016 according to Australia's Annual Overdose Report 2018.³ It is important to note that Tasmanian Government records show that the number of patients prescribed Schedule 8 opioids for persistent non-malignant pain increased from 1600 (2002) to 6400 (2016). While the Australian figures represent an unacceptable increase in preventable deaths, there has been a significant reduction in individual patient risk in Tasmania.

It should not be assumed this change was due solely to the implementation of DORA. In reality, the changes seen in Tasmania regarding these preventable deaths is more likely to have occurred following a significant increase in the rigour, sophistication and subsequent effectiveness of expert clinician-led, clinical governance regulatory activities and improvements in the awareness of GPs and pharmacists. These have been possible due to the efforts of local pain specialists, addiction specialists, pharmacists and GPs collaboratively providing advice to coordinate support to the clinical-regulatory pharmacists of the Tasmanian Government's Pharmaceutical Services Branch. Through these collective efforts, Tasmania has developed a robust, evidence-based, quality-assurance system that assists clinicians to safely and effectively treat patients via patient-and-clinician-specific audit-and-feedback mechanisms.⁴

DORA and the policies and procedures of the Pharmaceutical Services Branch have been the subject of as yet unpublished reviews conducted by Public Health Services Medical Registrars. Conclusions included 'DORA is contributing to a reduction in opioid-related harms in Tasmania, but the extent of the reduction could not be determined'.

Serious consideration needs to be given to all the options available to us to collectively tackle the injudicious prescribing of opioids. This is most often by a single medical practitioner or medical practice which time and again leads to what Tasmanian Coroner Carey in 2016 referred to as 'likely and avoidable' deaths.⁵ The time has come to refuse to accept these poisoning deaths as inevitable

'accidents', but rather acknowledge our collective failure to provide safe care.

Adoption of real-time monitoring throughout Australia might well avoid the high mortality from prescription opioid overdose currently reported in the USA. The Tasmanian clinical governance regulatory model of risk-based, targeted individual clinician accountability has improved standards of care in the clinical management of patients with chronic non-cancer pain. A persistent and consistent message has been communicated to clinicians about the importance of safe and appropriate treatment of patients with chronic non-cancer pain. This appears to be having an impact on clinical practice, for example the average prescribed oral morphine equivalent daily dose declined in Tasmania from 97.2 mg in 2004 to 35.1 mg

in 2017. It is our collective challenge to maintain and build on these evidence-guided improvements in clinical practice.

DORA has certainly proved to be a valuable tool for many clinicians. However, it is the partnership of expert clinicians in general practice, pain, and addiction medicine, working constructively with community and Tasmanian Government pharmacists, that has driven the change in the environment and clinical practice. This has resulted in better outcomes for the Tasmanian community and this partnership should be seriously considered by other Australian jurisdictions as part of their implementation of real-time monitoring. ◀

Conflict of interest: none declared

REFERENCES

1. Prescription Drug Monitoring Program Center of Excellence at Brandeis University. Briefing on PDMP Effectiveness. Updated Sep 2014. <http://www.pdmpassist.org/content/pdmp-evaluations> [cited 2019 Mar 1]
2. Turning Point, Eastern Health [Internet]. Dwyer J, presenter. Talking point: New insights into Victorian pharmaceutical drug overdose death. Talking Point Alcohol and Other Drug Seminar Series. 2017 Feb 22. www.turningpoint.org.au/education/talking-point/victorian-pharmaceutical-drug-overdose-death [cited 2019 Mar 1]
3. Pennington Institute. Australia's annual overdose report 2018. Melbourne: Pennington Institute; 2018. <http://www.pennington.org.au/australias-annual-overdose-report-2018> [cited 2019 Mar 1]
4. Pharmaceutical Services Branch, Tasmanian Government. Process for assessing and granting authorities to prescribe Schedule 8 drugs under Section 59E of the Tasmanian Poisons Act 1971. <https://www.dhhs.tas.gov.au/psbtas> [cited 2019 Mar 1]
5. Carey S, Coroner for Barnes, DJ. Record of investigation into death (without inquest). 2016 May 25. Magistrates Court of Tasmania, Coronial Division. https://www.magistratescourt.tas.gov.au/about_us/coroners/coronial_findings [cited 2019 Mar 1]



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Letters to the Editor

Dulaglutide efficacy

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I would like to bring to your attention an issue related to the new drug comment on dulaglutide for type 2 diabetes.¹

The conclusion, under the heading 'Place in therapy', states that 'Dulaglutide appears to have a greater effect on HbA1c than exenatide'. The reference given is the AWARD-1 trial, which to date is the only head-to-head study comparing the efficacy and safety of dulaglutide with placebo and exenatide.² However, in this trial the comparator was exenatide 10 microgram twice daily (not the once-weekly formulation of exenatide).

The article in its current form may mislead physicians to believe that dulaglutide was

demonstrated to be superior to the two available formulations of exenatide. To accurately reflect the current evidence, the comment should have said that dulaglutide appears to have a greater effect on HbA1c than exenatide 10 microgram twice daily. At present there is no evidence indicating greater efficacy of dulaglutide versus exenatide once weekly.

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REFERENCES

1. Dulaglutide for type 2 diabetes. *Aust Prescr* 2018;41:166-8. <https://doi.org/10.18773/austprescr.2018.052>
2. Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, Atisso C, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care* 2014;37:2159-67. <https://doi.org/10.2337/dc13-2760>

Influenza: overview on prevention and therapy

SUMMARY

Quadrivalent influenza vaccination is recommended annually for adults and children aged six months to 64 years.

High-dose or adjuvanted trivalent vaccines are recommended annually for people 65 years and over.

If started early enough, neuraminidase inhibitors reduce symptom duration by approximately one day. Treatment should be considered in patients with severe disease requiring hospitalisation or who are at risk of complications.

Chemoprophylaxis is not a substitute for vaccination but can be considered in high-risk individuals with an inadequate or ineffective vaccination status.

Introduction

Influenza causes considerable morbidity and mortality in Australia each year. Routine vaccination is the most important intervention for preventing illness and severe complications. Hand hygiene, cough etiquette and voluntary home isolation are also important factors in reducing transmission. The mainstay of treatment is symptom control and management of secondary complications. However, a number of antiviral drugs are available to treat influenza. They also have a small role in prophylaxis.

Preventing influenza

Influenza is a viral infection, mainly of the respiratory tract. There are two influenza A subtypes circulating in humans – A/H1N1 and A/H3N2 – and two influenza B subtypes – the Yamagata and Victoria lineages.

Annual vaccination is recommended for all individuals above six months of age (with the exception of any patients who have previously experienced anaphylaxis to the influenza vaccine or one of its components). Annual influenza vaccination is funded under the National Immunisation Program for people at increased risk of influenza morbidity and mortality. This includes the following:

- those over six months of age with medical risk factors
- Aboriginal and Torres Strait Islander children aged six months to five years
- Aboriginal and Torres Strait Islanders aged over 15 years
- all Australians aged over 65 years
- pregnant women.

Influenza in pregnancy is associated with an increased risk of maternal morbidity and mortality, along with preterm delivery. The influenza vaccine can be administered at any stage of pregnancy.

It is particularly important that healthcare providers in hospitals and general practices are vaccinated, given their likely exposure to individuals with influenza. This mitigates their potential for transmitting the virus, especially to people at risk of complications.

The antibody response to the vaccine takes approximately two weeks, with a period of optimal vaccine efficacy of around four months post vaccination. In Australia the seasonal influenza vaccine becomes available in March or April, and this is an appropriate time to vaccinate. The existence of several subtypes, along with seasonal antigenic changes, makes it difficult to predict which influenza strain will cause the most substantial burden of disease each year.

Given that the vaccine formulation is determined nine months before the influenza season, the strains included are based on the previous winter's circulating viruses, and are an informed prediction of what will be most prevalent in the coming season. Vaccine efficacy is variable from year to year and in different populations because of this.

Trivalent and quadrivalent vaccines

There is a range of different influenza vaccines available in Australia¹⁻⁷, some of which are provided through the National Immunisation Program (see Table).⁸ Trivalent vaccines cover the two influenza A types and a single B lineage whereas the quadrivalent vaccines cover the additional

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Table 2019 Australian seasonal influenza vaccines available on the National Immunisation Program

Type of vaccine	Age group	Brand name	Efficacy in clinical trials
Quadrivalent	6–35 months	FluQuadri Junior	The quadrivalent vaccines elicited non-inferior antibody responses to all A strains and corresponding B strains compared to a trivalent vaccine. Superior immunogenicity was shown for non-corresponding B strains in the quadrivalent vaccine. ¹
	3 years and over	FluQuadri	
	3 years and over	Fluarix Tetra	Fluarix Tetra elicited non-inferior antibody responses compared to the Fluarix trivalent vaccine and superior responses for the additional B strain not in the trivalent comparator. ²
	5 years and over	Afluria Quad	Afluria Quad elicited non-inferior immune responses to all comparator strains when compared to two trivalent vaccines containing alternate B strains. Superior immune responses to the trivalent unmatched strains were found. ⁴
Trivalent	65 years and over	Fluad (MF59-adjuvant)	Fluad (MF59-adjuvant) elicited significantly higher antibody responses compared to a non-adjuvanted trivalent vaccine in older people, including those with underlying medical conditions. Significantly higher responses were observed against heterologous A strains, and higher antibody responses were observed for H3N2 strains up to 12 months after vaccination. ⁶ A systematic review found that Fluad (MF59-adjuvant) was more effective than non-adjuvanted trivalent vaccine in preventing hospitalisation from pneumonia/influenza in older people (51%, 95% confidence interval 39–61%). ⁷

B virus lineage. There is evidence in the transition from trivalent to quadrivalent vaccines that the quadrivalent vaccines confer improved protection without any obvious increase in adverse reactions.⁹ The standard influenza vaccination for children and adults, including pregnant women, is now a single quadrivalent preparation. An exception to this is children aged six months to nine years who are receiving the vaccine for the first time, and those in the first year after receiving a solid organ or haematopoietic stem cell transplant. These patients should receive two doses at least four weeks apart to induce an optimal immune response.

High-dose and adjuvanted trivalent vaccines for older adults

People aged 65 and over have an increased risk of not only contracting influenza, but also of developing serious complications including heart attack, decompensated cardiac failure, pneumonia and death.^{10,11}

Two new trivalent vaccines for this age group were introduced in 2018, and one (Fluad) will be funded on the National Immunisation Program in 2019.⁸ They are currently not recommended for younger individuals, however recent literature suggests that recipients of solid organ transplants may also benefit from these vaccines.¹²

The high-dose preparation (Fluzone High-Dose) contains 60 microgram of the haemagglutinin antigen, which is four times more than the antigen content of other vaccine formulations for those under 65 years old. The adjuvanted vaccine (Fluad) contains MF-59,

a squalene-based emulsion that can rapidly induce antigen-specific CD4 responses. This results in strong and lasting T- and B-cell memory immune responses. The advantage of adjuvanted vaccines is they induce a broad host response while at the same time being dose sparing.

Recent studies have shown that administering trivalent flu vaccines, either at higher dose or with an adjuvant to increase immunogenicity, improves vaccine efficacy in people aged 65 or more.^{5,13–15} Other benefits include reduced hospitalisation for influenza and its complications, and reduced influenza-related deaths.^{13,16} A significantly higher rate of injection-site reactions has been reported with these preparations compared to standard trivalent vaccines (approximately 30% vs 20% of recipients). However, there has been no observed difference in the rate of serious adverse events.^{17,18}

The absence of the additional B lineage in these trivalent vaccines is not thought to be of notable detriment in older people for a number of reasons. First, the influenza A subtype A/H3N2 is likely to be responsible for the bulk of infections and serious complications in older patients. Second, a meta-analysis of several studies found that vaccination against a single influenza B strain confers up to 50% cross-protection against mismatched influenza B strains.¹⁹

At this stage, there have been no head-to-head trials comparing high-dose or adjuvanted trivalent vaccines with quadrivalent vaccination. New vaccine preparations (for example, using nanoparticles to carry influenza antigens) are under trial.

To date the safety and efficacy of adjuvanted or high-dose antigen influenza vaccines in pregnancy has not been established. Age-specific vaccine is recommended for pregnant women.

Antiviral drugs

There are two main classes of antiviral drugs that have been used for the treatment and prophylaxis of influenza – neuraminidase inhibitors and adamantanes. Multiple novel therapies are currently in development.

Neuraminidase inhibitors

Neuraminidase inhibitors are the mainstay of antiviral therapy against influenza. However, they need to be started within 48 hours of symptom onset and are most effective within 24 hours.

They inhibit the viral neuraminidase enzyme, preventing the virus from escaping the host cell.²⁰ Three neuraminidase inhibitors are currently registered in Australia – oral oseltamivir, inhaled zanamivir and intravenous peramivir.²¹

Efficacy

Oseltamivir shortens the duration of symptoms in uncomplicated influenza by approximately one day.^{22,23} The majority of studies were in healthy adults, and this effect has not been shown in asthmatic children.^{22,23} Inhaled zanamivir has shown a similar reduction in duration of symptoms in adults but has no significant effect in children.^{22,23} Single-dose intravenous peramivir is non-inferior to oseltamivir in adults and is a potential alternative for those who cannot take oral or inhaled medicines.²⁴

A newer long-acting neuraminidase inhibitor, laninamivir, achieves high concentrations in lung tissue with the potential to treat influenza following a single inhaled dose. It has comparable efficacy to oseltamivir in adults.^{25,26} An intravenous form of zanamivir has been recently studied in populations with severe influenza and also shows similar outcomes to oseltamivir.²⁷ While these two drugs are not currently registered in Australia, intravenous zanamivir has been used through the Special Access Scheme for critically ill patients with influenza.²¹

The role of neuraminidase inhibitors in reducing influenza complications is less clear.^{22,23} While oseltamivir has been shown to reduce unverified pneumonia, this has not been confirmed in trials with robust diagnostic criteria.²³ It has also not been shown to reduce the rate of hospital admissions.²²

Zanamivir has not been found to reduce pneumonia complications and its effect on hospital admissions has not been studied.^{22,23} In patients with influenza the use of neuraminidase inhibitors has been associated

with a mortality benefit, with delayed treatment resulting in increased mortality.²⁸

Recommendations for treatment

Prompt commencement of neuraminidase inhibitors is recommended for patients with confirmed or suspected influenza who require hospitalisation, or are at risk of complications (including children <5 years, adults ≥65 years, pregnant women, immunosuppressed patients or significant comorbidities), or have severe, complicated or progressive disease.²⁹⁻³¹ Therapy should begin within 48 hours of the onset of illness, but in severe disease treatment may still be beneficial if given outside this timeframe.^{28,30} Treatment should also be considered in those who have household contacts who are at high risk of influenza complications.^{30,31} The recommended duration of therapy (oseltamivir and zanamivir) is five days.²⁹ In healthy outpatients with uncomplicated influenza, treatment can be of limited benefit.^{29,30} Antibiotics are only indicated when patients have bacterial complications.^{29,31}

Antiviral resistance

Antiviral resistance has been well described in at-risk populations including immunocompromised hosts and young children due to a high virus burden and prolonged replication promoting resistance mutations.³² Factors that increase the risk of resistance include suboptimal antiviral dosing and cross-transmission of resistant strains in outbreaks.^{32,33} The H275Y mutation is commonly associated with oseltamivir-resistant influenza A strains, but laninamivir and zanamivir rarely show cross-resistance to strains expressing this mutation.³²

Adamantanes

Adamantanes work by inhibiting the M2 ion channel.²⁰ They are not recommended due to widespread resistance in circulating influenza viruses.^{20,29} Currently amantadine is the only drug to be registered in Australia for influenza. Its use is limited to prophylaxis of influenza A.^{21,34} When used for treatment, amantadine shortens the duration of fever by approximately one day, but has no effect on nasal shedding or upper airways viral clearance.³⁴

Antiviral prophylaxis

There is a role for neuraminidase inhibitors in prophylaxis. Oseltamivir and zanamivir are approved in Australia for this and have shown to significantly reduce the risk of symptomatic influenza.^{22,23} However, chemoprophylaxis should not be considered as an alternative to vaccination.²⁹

For individual benefit, post-exposure prophylaxis with neuraminidase inhibitors should be considered for

contacts who are at high risk of influenza complications and cannot be (or have not been) vaccinated or are likely to have an inadequate or ineffective vaccine response.³⁰ In household settings, chemoprophylaxis can be considered for remaining contacts of a suspected or confirmed influenza case, if there is another member at high risk of influenza complications.³⁰

During an influenza outbreak in residential care facilities (including aged care, correctional facilities, hostels), antiviral prophylaxis should only be considered in addition to other infection control measures. The decision to administer antivirals must be made in collaboration with treating doctors, public health authorities and the local outbreak management team.³⁵ When used, antiviral prophylaxis should be started within 24 hours of declaring an outbreak for all asymptomatic residents (regardless of vaccination status) and all unvaccinated staff.^{30,35} Chemoprophylaxis should be continued for 10 days or until the outbreak is over, whichever is longer.³⁵ There may be a role to extend this approach of antiviral 'ring prophylaxis' in other closed or semi-closed environments (i.e. cruise ships, military barracks, boarding schools) where antiviral prophylaxis in close contacts may truncate the spread of infection.^{35,36}

Antiviral prophylaxis has also been shown to be effective in inpatient settings, particularly for immunocompromised patients.³⁷

Limitations of influenza prophylaxis

Chemoprophylaxis does not completely eliminate the risk of influenza and susceptibility to infection returns once antiviral prophylaxis is stopped.²⁹

In an outbreak, neuraminidase inhibitors may be ineffective at preventing asymptomatic influenza (meaning transmission may still occur). In the long term, chemoprophylaxis may result in the emergence of influenza viruses with reduced susceptibility to these drugs.^{22,23,32}

Novel therapies

Several novel therapies are being developed for influenza treatment. These target various stages of influenza infection including prevention of viral entry (DAS181-F03), fusion with host cells (Arbidol), viral transcription and replication (Favipiravir, Pimodovir, S 033188) and maturation of key viral proteins (nitazoxanide).^{38,39} There are also several monoclonal antibodies being developed that target viral structures, primarily haemagglutinin, to neutralise the virus.³⁸ Combination therapy with oseltamivir, amantadine, and ribavirin has also been studied but has shown no clinical benefit over oseltamivir alone.⁴⁰

Conclusion

Influenza infection is an important public health problem, with a substantial disease burden in Australia and worldwide. Vaccination is the most important tool in influenza prevention. Current antiviral therapies have a modest effect on symptom duration with no effect on viral shedding or disease complications. Ongoing research is required to develop more effective therapies and combat emerging antiviral resistance. ◀

REFERENCES

- Greenberg DP, Robertson CA, Landolfi VA, Bhaumik A, Senders SD, Decker MD. Safety and immunogenicity of an inactivated quadrivalent influenza vaccine in children 6 months through 8 years of age. *Pediatr Infect Dis J* 2014;33:630-6. <https://doi.org/10.1097/INF.0000000000000254>
- Kieninger D, Sheldon E, Lin WY, Yu CJ, Bayas JM, Gabor JJ, et al. Immunogenicity, reactogenicity and safety of an inactivated quadrivalent influenza vaccine candidate versus inactivated trivalent influenza vaccine: a phase III, randomized trial in adults aged ≥18 years. *BMC Infect Dis* 2013;13:343. <https://doi.org/10.1186/1471-2334-13-343>
- van de Witte S, Nauta J, Montomoli E, Weckx J. A phase III randomised trial of the immunogenicity and safety of quadrivalent versus trivalent inactivated subunit influenza vaccine in adult and elderly subjects, assessing both anti-haemagglutinin and virus neutralisation antibody responses. *Vaccine* 2018;36:6030-8. <https://doi.org/10.1016/j.vaccine.2018.04.043>
- Treanor JT, Albano FR, Sawlwin DC, Graves Jones A, Airey J, Formica N, et al. Immunogenicity and safety of a quadrivalent inactivated influenza vaccine compared with two trivalent inactivated influenza vaccines containing alternate B strains in adults: a phase 3, randomized noninferiority study. *Vaccine* 2017;35:1856-64. <https://doi.org/10.1016/j.vaccine.2017.02.066>
- DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med* 2014;371:635-45. <https://doi.org/10.1056/NEJMoal315727>
- Frey SE, Reyes MR, Reynales H, Bernal NN, Nicolay U, Narasimhan V, et al. Comparison of the safety and immunogenicity of an MF59®-adjuvanted with a non-adjuvanted seasonal influenza vaccine in elderly subjects. *Vaccine* 2014;32:5027-34. <https://doi.org/10.1016/j.vaccine.2014.07.013>
- Domnich A, Arata L, Amicizia D, Puig-Barberà J, Gasparini R, Panatto D. Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: a systematic review and meta-analysis. *Vaccine* 2017;35:513-20. <https://doi.org/10.1016/j.vaccine.2016.12.011>
- Australian Government Department of Health, Statement from the Chief Medical Officer. 2019 influenza vaccines [Internet]. <https://beta.health.gov.au/news-and-events/media-releases/2019-influenza-vaccines> [cited 2019 Mar 14]
- Greenberg DP, Robertson CA, Noss MJ, Blatter MM, Biedenbender R, Decker MD. Safety and immunogenicity of a quadrivalent inactivated influenza vaccine compared to licensed trivalent inactivated influenza vaccines in adults. *Vaccine* 2013;31:770-6. <https://doi.org/10.1016/j.vaccine.2012.11.074>
- Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, et al. Influenza-associated hospitalizations in the United States. *JAMA* 2004;292:1333-40. <https://doi.org/10.1001/jama.292.11.1333>
- Sandoval C, Walter SD, Krueger P, Smieja M, Smith A, Yusuf S, et al. Risk of hospitalization during influenza season among a cohort of patients with congestive heart failure. *Epidemiol Infect* 2007;135:574-82. <https://doi.org/10.1017/S095026880600714X>
- Natori Y, Shiotsuka M, Slomovic J, Hoschler K, Ferreira V, Ashton P, et al. A double-blind, randomized trial of high-dose vs standard-dose influenza vaccine in adult solid-organ transplant recipients. *Clin Infect Dis* 2018;66:1698-704. <https://doi.org/10.1093/cid/cix1082>
- Mannino S, Villa M, Apolone G, Weiss NS, Groth N, Aquino I, et al. Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy. *Am J Epidemiol* 2012;176:527-33. <https://doi.org/10.1093/aje/kws313>

14. Izurieta HS, Thadani N, Shay DK, Lu Y, Maurer A, Foppa IM, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. *Lancet Infect Dis* 2015;15:293-300. [https://doi.org/10.1016/S1473-3099\(14\)71087-4](https://doi.org/10.1016/S1473-3099(14)71087-4)
15. Gravenstein S, Davidson HE, Taljaard M, Ogarek J, Gozalo P, Han L, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. *Lancet Respir Med* 2017;5:738-46. [https://doi.org/10.1016/S2213-2600\(17\)30235-7](https://doi.org/10.1016/S2213-2600(17)30235-7)
16. Shay DK, Chillarige Y, Kelman J, Forshee RA, Foppa IM, Werneck M, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines among US Medicare beneficiaries in preventing postinfluenza deaths during 2012-2013 and 2013-2014. *J Infect Dis* 2017;215:510-7. <https://doi.org/10.1093/infdis/jiw641>
17. Kaka AS, Filice GA, Myllybeck S, Nichol KL. Comparison of side effects of the 2015-2016 high-dose, inactivated, trivalent influenza vaccine and standard dose, inactivated, trivalent influenza vaccine in adults ≥65 years. *Open Forum Infect Dis* 2017;4:ofx001. <https://doi.org/10.1093/ofid/ofx001>
18. Villa M, Black S, Groth N, Rothman KJ, Apolone G, Weiss NS, et al. Safety of MF59-adjuvanted influenza vaccination in the elderly: results of a comparative study of MF59-adjuvanted vaccine versus nonadjuvanted influenza vaccine in northern Italy. *Am J Epidemiol* 2013;178:1139-45. <https://doi.org/10.1093/aje/kwt078>
19. Tricco AC, Chit A, Soobiah C, Hallett D, Meier G, Chen MH, et al. Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis. *BMC Med* 2013;11:153. <https://doi.org/10.1186/1741-7015-11-153>
20. Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's principles and practices of infectious diseases. 8th ed. Philadelphia, PA: Elsevier; 2015.
21. Therapeutic Goods Administration. Australian Register of Therapeutic Goods [Internet]. www.tga.gov.au/artg [cited 2019 Mar 1]
22. Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2014;CD008965. <https://doi.org/10.1002/14651858.CD008965.pub4>
23. Heneghan CJ, Onakpoya I, Jones MA, Doshi P, Del Mar CB, Hama R, et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. *Health Technol Assess* 2016;20:1-242. <https://doi.org/10.3310/hta20420>
24. Kohno S, Yen MY, Cheong HJ, Hirotsu N, Ishida T, Kadota J, et al.; S-021812 Clinical Study Group. Phase III randomized, double-blind study comparing single-dose intravenous peramivir with oral oseltamivir in patients with seasonal influenza virus infection. *Antimicrob Agents Chemother* 2011;55:5267-76. <https://doi.org/10.1128/AAC.00360-11>
25. Koyama K, Takahashi M, Oitate M, Nakai N, Takakusa H, Miura S, et al. CS-8958, a prodrug of the novel neuraminidase inhibitor R-125489, demonstrates a favorable long-retention profile in the mouse respiratory tract. *Antimicrob Agents Chemother* 2009;53:4845-51. <https://doi.org/10.1128/AAC.00731-09>
26. Watanabe A, Chang SC, Kim MJ, Chu DW, Ohashi Y; MARVEL Study Group. Long-acting neuraminidase inhibitor laninamivir octanoate versus oseltamivir for treatment of influenza: a double-blind, randomized, noninferiority clinical trial. *Clin Infect Dis* 2010;51:1167-75. <https://doi.org/10.1086/656802>
27. Marty FM, Vidal-Puigserver J, Clark C, Gupta SK, Merino E, Garot D, et al. Intravenous zanamivir or oral oseltamivir for hospitalised patients with influenza: an international, randomised, double-blind, double-dummy, phase 3 trial. *Lancet Respir Med* 2017;5:135-46. [https://doi.org/10.1016/S2213-2600\(16\)30435-0](https://doi.org/10.1016/S2213-2600(16)30435-0)
28. Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Al Khuwaitir TS, Al Mamun A, et al.; PRIDE Consortium Investigators. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med* 2014;2:395-404. [https://doi.org/10.1016/S2213-2600\(14\)70041-4](https://doi.org/10.1016/S2213-2600(14)70041-4)
29. Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM; Centers for Disease Control and Prevention (CDC). Antiviral agents for the treatment and chemoprophylaxis of influenza --- recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2011;60:1-24.
30. Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, et al.; Expert Panel of the Infectious Diseases Society of America. Seasonal influenza in adults and children--diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2009;48:1003-32. <https://doi.org/10.1086/598513>
31. Antibiotic. In ETG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2019. www.tg.org.au [cited 2019 Mar 1]
32. Li TC, Chan MC, Lee N. Clinical implications of antiviral resistance in influenza. *Viruses* 2015;7:4929-44. <https://doi.org/10.3390/v7092850>
33. Moore C, Galiano M, Lackenby A, Abdelrahman T, Barnes R, Evans MR, et al. Evidence of person-to-person transmission of oseltamivir-resistant pandemic influenza A(H1N1) 2009 virus in a hematology unit. *J Infect Dis* 2011;203:18-24. <https://doi.org/10.1093/infdis/jiq007>
34. Jefferson T, Demicheli V, Di Pietrantonj C, Rivetti D. Amantadine and rimantadine for influenza A in adults. *Cochrane Database Syst Rev* 2006;CD001169. <https://doi.org/10.1002/14651858.CD001169.pub3>
35. Communicable Diseases Network of Australia (CDNA). Guidelines for the prevention, control and public health management of influenza outbreaks in residential care facilities in Australia [Internet]. Canberra: Department of Health; 2017. www.health.gov.au/internet/main/publishing.nsf/Content/cdna-flu-guidelines.htm [cited 2019 Mar 1]
36. Lee VJ, Yap J, Cook AR, Chen MI, Tay JK, Tan BH, et al. Oseltamivir ring prophylaxis for containment of 2009 H1N1 influenza outbreaks. *N Engl J Med* 2010;362:2166-74. <https://doi.org/10.1056/NEJMoa0908482>
37. Yue MC, Collins JT, Subramoniapillai E, Kennedy GA. Successful use of oseltamivir prophylaxis in managing a nosocomial outbreak of influenza A in a hematology and allogeneic stem cell transplant unit. *Asia Pac J Clin Oncol* 2017;13:37-43. <https://doi.org/10.1111/ajco.12565>
38. Koszalka P, Tilmanis D, Hurt AC. Influenza antivirals currently in late-phase clinical trial. *Influenza Other Respir Viruses* 2017;11:240-6. <https://doi.org/10.1111/irv.12446>
39. Boriskin YS, Leneva IA, Pecher EI, Polyak SJ, et al. Arbidol: a broad-spectrum antiviral compound that blocks viral fusion. *Curr Med Chem* 2008;15:997-1005. <https://doi.org/10.2174/092986708784049658>
40. Beigel JH, Bao Y, Beeler J, Manosuthi W, Slandzicki A, Dar SM, et al.; IRC003 Study Team. Oseltamivir, amantadine, and ribavirin combination antiviral therapy versus oseltamivir monotherapy for the treatment of influenza: a multicentre, double-blind, randomised phase 2 trial. *Lancet Infect Dis* 2017;17:1255-65. [https://doi.org/10.1016/S1473-3099\(17\)30476-0](https://doi.org/10.1016/S1473-3099(17)30476-0)

FURTHER READING

Australian Technical Advisory Group on Immunisation. Australian immunisation handbook [Internet]. Canberra: Department of Health; 2018. <https://immunisationhandbook.health.gov.au> [cited 2019 Mar 1]

Foo H, Dwyer DE. Rapid tests for the diagnosis of influenza. *Aust Prescr* 2009;32:64-7. <https://doi.org/10.18773/austprescr.2009.034>

Drug-induced movement disorders

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SUMMARY

Many therapeutic and illicit drugs can cause movement disorders. Antipsychotics and antiemetics are most commonly implicated.

The time of onset of the movement disorder may be acute, subacute, or chronic. The severity can range from mild to severe and life-threatening.

Early recognition of a drug-induced movement disorder is essential to allow for prompt intervention. This includes stopping the offending drug, supportive care, and sometimes other pharmacological treatment.

Introduction

Both therapeutic and illicit drugs can cause neurological adverse effects, including movement disorders. The most common causes of drug-induced movement disorders are dopamine receptor blocking drugs, including antipsychotics and antiemetics (Table 1). Drug-induced movement disorders can range from tremors to life-threatening syndromes. They can be classified chronologically based on the time of onset after drug ingestion, as acute, subacute or tardive.

Acute disorders

Acute drug-induced movement disorders occur within minutes to days of drug ingestion. They include akathisia, tremor, neuroleptic malignant syndrome, serotonin syndrome, parkinsonism-hyperpyrexia disorder and acute dystonic reactions.^{1–4}

Akathisia

Akathisia is a common, but often under-recognised, drug-induced movement disorder that can occur as an acute, subacute or tardive reaction. It is a sense of internal restlessness, irritability and tension without necessarily manifesting with physical signs, unlike restless legs syndrome which is typically more severe and worse at night. Akathisia has been reported with dopamine receptor blockers, selective serotonin reuptake inhibitors (SSRIs), antiepileptic drugs, and cocaine. It can occur either after starting a dopamine receptor blocker, dose escalation, or when switching to an alternative drug.

Akathisia often improves following cessation of the offending drug. Anticholinergics, beta blockers, benzodiazepines, amantadine, mirtazapine and clonidine have also been used with varying efficacy and with minimal evidence.

Tremor

Drug-induced tremor is typically postural or kinetic, or both. It is symmetrical and occurs acutely following drug ingestion or dose escalation. Exceptions include tremor secondary to valproate, which can appear at therapeutic or during stable treatment, or, rarely, tardive tremor. Tremor can occur secondary to many drugs, including SSRIs, lithium, tricyclic antidepressants, antiepileptics (particularly valproate), bronchodilators, amiodarone and immunosuppressives. Another underlying aetiology, such as Parkinson's disease, essential tremor or hyperthyroidism, needs to be excluded.

Management consists of altering the dose of, or if possible stopping, the offending drug, or switching to an alternative drug. Should the offending drug need to be continued, discuss the risks of the adverse effects versus the benefits of continuing to ensure the patient is informed. If the drug is continued, drugs typically used for essential tremor (for example, propranolol) can occasionally be beneficial.

Serotonin syndrome

Serotonin syndrome occurs secondary to drugs that increase serotonin activity (Table 1). Like neuroleptic malignant syndrome, it can be life-threatening, but milder forms can occur. Clinical characteristics include:

- altered mental status
- signs of central nervous system hyperexcitability
 - movement disorders, including myoclonus, tremor, akathisia
 - hyperreflexia, clonus, spasticity or rigidity, seizures
- autonomic instability, including mydriasis, fever and tachycardia.

Table 1 Drug-induced movements disorders

Movement disorder	Implicated drugs
Akathisia	Dopamine receptor blocking drugs Selective serotonin reuptake inhibitors Antiepileptics
Tremor	Selective serotonin reuptake inhibitors Lithium Tricyclic antidepressants Antiepileptics (e.g. valproate) Bronchodilators Amiodarone Immunosuppressive drugs (tacrolimus, ciclosporin)
Serotonin syndrome (usually due to overdose or combinations of serotonergic drugs)	Selective serotonin reuptake inhibitors Serotonin noradrenaline reuptake inhibitors Tricyclic antidepressants Monoamine oxidase inhibitors Lithium Linezolid Opioids (pethidine, tramadol, propentadol) Antiepileptics (valproate, lamotrigine) St John's wort
Acute dystonic reaction	Dopamine receptor blocking drugs (e.g. antipsychotics, metoclopramide) Selective serotonin reuptake inhibitors Opioids Methylphenidate Rivastigmine Albendazole Gabapentin Cetirizine Foscarnet Quinine Propofol Sevoflurane
Neuroleptic malignant syndrome	Antipsychotics (e.g. haloperidol, fluphenazine, chlorpromazine) Prochlorperazine Metoclopramide Droperidol Promethazine Tetrabenazine Lithium
Parkinsonism	Dopamine receptor blocking drugs (e.g. antipsychotics) Calcium channel antagonists (e.g. flunarizine, cinnarizine) Antiepileptics (e.g. phenytoin, valproate, levetiracetam) Antidepressants (e.g. selective serotonin reuptake inhibitors, monoamine oxidase inhibitors) Lithium Chemotherapeutic drugs (e.g. cytosine arabinoside, cyclophosphamide, vincristine, adriamycin, doxorubicin, paclitaxel, etoposide) Immunosuppressive drugs (e.g. ciclosporin, tacrolimus) Toxins (e.g. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), organophosphate pesticides, manganese, methanol, cyanide, carbon monoxide and carbon disulphide)
Tardive drug-induced movement disorders	Antipsychotics Antiemetics (e.g. metoclopramide)

The altered mental status, autonomic instability, and spasticity or rigidity with raised creatine kinase, overlap with neuroleptic malignant syndrome. In serotonin syndrome the onset is hyperacute, within hours rather than days, and the signs of central nervous system hyperexcitability are more prominent.

Management

Discontinuation of the offending drugs and supportive care (which may include intensive care) are first-line in treating serotonin syndrome. Cyproheptadine may be given in less severe cases and, if a response is observed, it should be continued until symptoms resolve.⁵ Benzodiazepines or other 5-hydroxytryptamine 2 receptor antagonists (such as chlorpromazine or olanzapine) have been used in severe cases.^{4,5}

Parkinsonism-hyperpyrexia disorder

Parkinsonism-hyperpyrexia disorder, also known as akinetic crisis, is a rare but potentially fatal complication of Parkinson's disease. It involves a syndrome of significantly worsening parkinsonism (with or without encephalopathy), hyperpyrexia, autonomic instability and elevated creatine kinase.⁴⁻⁶ The disorder is most commonly seen in patients with Parkinson's disease who have reduced or stopped their antiparkinsonian drugs. It can also be precipitated by an infection or other metabolic disturbance. The clinical features overlap with neuroleptic malignant syndrome. It is also important to exclude alternative causes, including an underlying infection, metabolic abnormalities, or stroke. Recovery can take hours to weeks following treatment.

Management

The mainstay of treatment includes resuming anti-parkinsonian drugs, usually via nasogastric tube because of the dysphagia resulting from severe parkinsonism. Intermittent apomorphine injections or a continuous infusion may be required in moderate-severe cases.

Acute dystonic reactions

Acute dystonic reactions most commonly occur in younger patients soon after taking dopamine receptor blocking drugs, including antiemetics (e.g. metoclopramide or prochlorperazine) and antipsychotics. Acute sustained dystonic spasm of craniocervical muscles is typical, but oculogyric crises, truncal spasm causing opisthotonos, or limb dystonia can also occur. Acute laryngeal dystonia can be life-threatening due to airway obstruction and requires emergency medical care.

Management

Stop the offending drug, and give an intravenous or intramuscular anticholinergic drug (such as benztropine or trihexyphenidyl (benzhexol) hydrochloride). As the injectable drug has a short half-life it is followed by a short course of oral anticholinergic drugs.^{4,5,7} Benzodiazepines have also been used. It is important to avoid the offending drug in the future due to the risk of a recurrent dystonic reaction. Educate the patient regarding this risk.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome is a potentially life-threatening reaction to typical and atypical antipsychotic drugs and other dopamine receptor blocking drugs, including tetrabenazine, lithium and antiemetics such as metoclopramide. Delphi consensus diagnostic criteria⁸ have been recently validated.⁹ These criteria include:

- exposure to a dopamine antagonist, or dopamine agonist withdrawal, within the past 72 hours
- hyperthermia (>38 °C on at least two occasions)
- rigidity
- altered mental status
- elevated creatine kinase
- autonomic instability (including hypermetabolism, i.e. tachycardia and tachypnoea)
- negative investigations for an alternative cause.

In addition to the elevated creatine kinase, laboratory investigations usually find leucocytosis, abnormal electrolytes, renal impairment, abnormal liver function tests, and altered coagulation studies. Milder cases without all the clinical features can occur.

There are a number of differential diagnoses, including serotonin syndrome, and specialist assessment is required. For example, serotonin syndrome tends to occur more acutely than neuroleptic malignant syndrome. There is rigidity in neuroleptic malignant syndrome whereas myoclonus, hyperreflexia with clonus, and mydriasis are more common in serotonin syndrome.

Management

If neuroleptic malignant syndrome is suspected, acute hospital admission is warranted. Management involves immediate cessation of the offending drugs, supportive care (which includes intensive care if severe), and giving a dopaminergic drug, usually bromocriptine. Subcutaneous apomorphine injections have also been used. Benzodiazepines can be used to reduce rhabdomyolysis and improve rigidity.

The syndrome typically plateaus and improves within 2–3 weeks of onset. Bromocriptine should therefore be continued for several weeks to ensure the syndrome has completely subsided. Consideration about restarting an antipsychotic requires a specialist psychiatric opinion.

Subacute disorders

Subacute drug-induced movement disorders occur within days to weeks of drug ingestion. Some of the syndromes listed in Table 1 can develop subacutely. They usually respond to cessation of the offending drug.

Parkinsonism

Drug-induced parkinsonism is typically characterised by bradykinesia, rigidity and postural instability. It is the second commonest cause of parkinsonism after idiopathic Parkinson's disease. Various drugs have been associated with parkinsonism (see Table 1).

In contrast to idiopathic Parkinson's disease, drug-induced parkinsonism usually presents as a symmetrical akinetic rigid syndrome which develops over days to weeks to months following ingestion of the offending drug. Additionally, there is a poor response to typical antiparkinsonian drugs, including levodopa, dopamine agonists and anticholinergic drugs. Cessation of the offending drug usually results in complete resolution of the disorder.

Additionally, toxins can cause parkinsonism. These include 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), organophosphate pesticides, manganese, methanol, cyanide, carbon monoxide, and carbon disulphide. Unlike the drugs, toxins are often associated with irreversible structural damage to the basal ganglia visible on MRI.

Levodopa-induced dyskinesia

Levodopa-induced dyskinesia is a common cause of dyskinesia in individuals with Parkinson's disease. It occurs due to the relationship between dopaminergic loss and the resultant response to levodopa, rather than being due to excess levodopa ingestion only. Risk factors for developing dyskinesia include young age at onset of Parkinson's disease, higher levodopa dose, low body weight, and more severe disease.¹⁰ A careful history is vital in establishing a pattern to the timing and duration of dyskinesias, which can then assist in altering the levodopa dose.

Depending on the duration of dyskinesia, the levodopa dose can usually be reduced to a lower dose which still maintains efficacy. It is worth noting that mild dyskinesias are often not bothersome to the individual and do not interfere with their function, therefore a change in levodopa dose may

not be required. Amantadine can also be used to manage levodopa-induced dyskinesias. Referral is recommended for patients with late-stage disease for consideration of device-assisted therapy.

Tardive disorders

Tardive drug-induced movement disorders occur either during exposure or within weeks of stopping a drug and are present for at least one month.^{1,11–14}

The minimum duration of exposure to the drug is three months, or one month in adults aged over 60 years. The most commonly implicated drugs include antipsychotics, antiemetics (metoclopramide and prochlorperazine) and some calcium channel antagonists with dopamine receptor blocking properties (cinnarizine and flunarizine).

Tardive movement disorders include dyskinesias (typically orobuccolingual), stereotypies, akathisia, dystonia (focal, segmental or generalised), myoclonus, tremor and tics. Additionally, tardive parkinsonism may be experienced. Withdrawal-emergent dyskinesia can occur on abrupt cessation of long-term antipsychotic treatment, particularly in children. The dyskinesia improves on resuming the drug. The dose can then be gradually reduced.

Management

No good evidence exists regarding the management of tardive drug-induced movement disorders.¹⁵ Treatment usually consists of withdrawing the offending drug, and a trial of a combination of drugs. Clonazepam has been effective particularly for myoclonus. Resuming the offending drug or changing to an atypical antipsychotic is sometimes required.¹⁶ In patients with a chronic psychotic disorder clozapine is preferred. Most recently, vesicular monoamine transporter 2 inhibitors deutetrabenazine and valbenazine have been proposed as treatment options.^{17,18} Other oral drugs have been tried, including tetrabenazine, amantadine and propranolol.

Antioxidants, including vitamin E, vitamin B₆ and *Ginkgo biloba*, have also been studied. Vitamin E had conflicting results, while vitamin B₆ and *Ginkgo biloba* are probably useful in treating tardive movement disorders.^{17,18} Caution is needed with *Ginkgo biloba* because of its antiplatelet effects, especially in patients taking antiplatelet drugs or anticoagulants. Anticholinergic drugs to prevent, or reduce the severity of, drug-induced movement disorders have been suggested, however there is no evidence to support this.

Botulinum toxin injections can be effective for focal manifestations of tardive dystonia.¹⁹ Deep brain stimulation, targeting the globus pallidus, can be highly effective in severe cases.²⁰

ARTICLE

Drug-induced movement disorders



SELF-TEST
QUESTIONS

True or false?

1. Antiemetics can cause neuroleptic malignant syndrome.
2. Levodopa should be stopped if a patient with Parkinson's disease develops parkinsonism-hyperpyrexia disorder.

Answers on page 79

Illicit drugs

Movement disorders secondary to illicit drugs are usually acute and self-limiting,^{4,21} but can occasionally be life-threatening (Table 2). Cocaine blocks dopamine reuptake thereby increasing dopaminergic drive. Amphetamines cause more widespread catecholaminergic stimulation, but chronic use results in dopamine depletion, and is possibly associated with nigral damage.²² 3,4-methylenedioxymethamphetamine (MDMA) is known to cause parkinsonism and a syndrome similar to serotonin syndrome.

While the movement disorder usually occurs following drug ingestion, it can also occur during the withdrawal phase. Typically, it subsides on cessation of the drug, but can last for months. No specific treatment exists for movement disorders caused by illicit drug use.

Conclusion

Movement disorders are a common, and at times life-threatening, adverse effect of many drugs,

most commonly dopamine receptor blocking drugs. Patients are often on combinations of drugs that may cause more than one movement disorder, thereby making it challenging to identify the culprit drug. The diagnosis requires knowledge of the typical movement disorders and the syndromes that can occur with different drug classes, and their typical time course. This is important because the most imperative therapeutic intervention for most drug-induced movement disorders is stopping the offending drug, with or without supportive or other pharmacological treatment. ◀

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Table 2 Illicit drugs and associated movement disorders

Drug	Movement disorder
Cocaine	Choreoathetosis (chorea and dystonia, also known as 'crack dancing') Stereotypies Tremor Myoclonus
Amphetamines	Punding (purposeless, repetitive behaviours) Tremor Dystonia Choreoathetosis Orolingual dyskinesia
3,4-methylenedioxymethamphetamine (MDMA)	Serotonin syndrome Parkinsonism
Opioids	Myoclonus

REFERENCES

1. Claxton KL, Chen JJ, Swope DM. Drug-induced movement disorders. J Pharm Pract 2007;20:415-29. <https://doi.org/10.1177/0897190007310514>
2. Malek N, Baker MR. Common toxidromes in movement disorder neurology. Postgrad Med J 2017;93:326-32. <https://doi.org/10.1136/postgradmedj-2016-134254>
3. Caroff SN, Campbell EC. Drug-induced extrapyramidal syndromes: implications for contemporary practice. Psychiatr Clin North Am 2016;39:391-411. <https://doi.org/10.1016/j.psc.2016.04.003>
4. Burkhard PR. Acute and subacute drug-induced movement disorders. Parkinsonism Relat Disord 2014;20 Suppl 1:S108-12. [https://doi.org/10.1016/S1353-8020\(13\)70027-0](https://doi.org/10.1016/S1353-8020(13)70027-0)
5. Kipps CM, Fung VS, Grattan-Smith P, de Moore GM, Morris JG. Movement disorder emergencies. Mov Disord 2005;20:322-34. <https://doi.org/10.1002/mds.20325>
6. Newman EJ, Grosset DG, Kennedy PG. The parkinsonism-hyperpyrexia syndrome. Neurocrit Care 2009;10:136-40. <https://doi.org/10.1007/s12028-008-9125-4>
7. Marano M, di Biase L, Salomone G, Di Santo A, Montiroli A, Di Lazzaro V. The clinical course of a drug-induced acute dystonic reaction in the emergency room. Tremor Other Hyperkinet Mov (N Y) 2016;6:436. <https://doi.org/10.7916/D87P8ZS1>
8. Gurrera RJ, Caroff SN, Cohen A, Carroll BT, DeRoos F, Francis A, et al. An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method. J Clin Psychiatry 2011;72:1222-8. <https://doi.org/10.4088/JCP.10m06438>
9. Gurrera RJ, Mortillaro G, Velamoor V, Caroff SN. A validation study of the international consensus diagnostic criteria for neuroleptic malignant syndrome. J Clin Psychopharmacol 2017;37:67-71. <https://doi.org/10.1097/JCP.0000000000000640>

10. Warren Olanow C, Kieburtz K, Rascol O, Poewe W, Schapira AH, Emre M, et al.; Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) Investigators. Factors predictive of the development of levodopa-induced dyskinesia and wearing-off in Parkinson's disease. *Mov Disord* 2013;28:1064-71. <https://doi.org/10.1002/mds.25364>
11. Aquino CC, Lang AE. Tardive dyskinesia syndromes: current concepts. *Parkinsonism Relat Disord* 2014;20 Suppl 1:S113-7. [https://doi.org/10.1016/S1353-8020\(13\)70028-2](https://doi.org/10.1016/S1353-8020(13)70028-2)
12. Cornett EM, Novitch M, Kaye AD, Kata V, Kaye AM. Medication-induced tardive dyskinesia: a review and update. *Ochsner J* 2017;17:162-74.
13. Frei K, Truong DD, Fahn S, Jankovic J, Hauser RA. The nosology of tardive syndromes. *J Neurol Sci* 2018;389:10-6. <https://doi.org/10.1016/j.jns.2018.02.008>
14. Savitt D, Jankovic J. Tardive syndromes. *J Neurol Sci* 2018;389:35-42. <https://doi.org/10.1016/j.jns.2018.02.005>
15. Bhidayasiri R, Fahn S, Weiner WJ, Gronseth GS, Sullivan KL, Zesiewicz TA; American Academy of Neurology. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2013;81:463-9. <https://doi.org/10.1212/WNL.0b013e31829d86b6>
16. Mentzel CL, Bakker PR, van Os J, Drukker M, Matroos GE, Hoek HW, et al. Effect of antipsychotic type and dose changes on tardive dyskinesia and parkinsonism severity in patients with a serious mental illness: the Curacao extrapyramidal syndromes study XII. *J Clin Psychiatry* 2017;78:e279-85. <https://doi.org/10.4088/JCP.16m11049>
17. Niemann N, Jankovic J. Treatment of tardive dyskinesia: a general overview with focus on the vesicular monoamine transporter 2 inhibitors. *Drugs* 2018;78:525-41. <https://doi.org/10.1007/s40265-018-0874-x>
18. Bhidayasiri R, Jitkriksadikul O, Friedman JH, Fahn S. Updating the recommendations for treatment of tardive syndromes: a systematic review of new evidence and practical treatment algorithm. *J Neurol Sci* 2018;389:67-75. <https://doi.org/10.1016/j.jns.2018.02.010>
19. Jankovic J. An update on new and unique uses of botulinum toxin in movement disorders. *Toxicon* 2018;147:84-8. <https://doi.org/10.1016/j.toxicon.2017.09.003>
20. Macerollo A, Deuschl G. Deep brain stimulation for tardive syndromes: systematic review and meta-analysis. *J Neurol Sci* 2018;389:55-60. <https://doi.org/10.1016/j.jns.2018.02.013>
21. Asser A, Taba P. Psychostimulants and movement disorders. *Front Neurol* 2015;6:75. <https://doi.org/10.3389/fneur.2015.00075>
22. Lappin JM, Darke S, Farrell M. Methamphetamine use and future risk for Parkinson's disease: evidence and clinical implications. *Drug Alcohol Depend* 2018;187:134-40. <https://doi.org/10.1016/j.drugalcdep.2018.02.032>

FURTHER READING

Jamshidi N, Dawson A. The hot patient: acute drug-induced hyperthermia. *Aust Prescr* 2019;42:24-8. <https://doi.org/10.18773/austprescr.2019.006>

Immune checkpoint inhibitors in malignancy

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SUMMARY

Immune checkpoints normally stop the body from mounting an immune response against healthy cells. Some cancers can acquire these checkpoints so that the tumour cells are not recognised by the immune system.

Inhibiting the checkpoints therefore enables the tumour cells to be recognised and allows an immune response to be activated against them.

Immune checkpoint inhibitors can improve the survival of some patients with advanced malignancies. These include malignant melanoma, renal cell carcinoma, urothelial bladder cancer and non-small cell lung cancer.

Trials have shown that immune checkpoint inhibitors have significant benefits over conventional therapies so they are increasingly being used in routine clinical practice.

However, a significant proportion of patients will not respond to immune checkpoint inhibitors and retain a poor prognosis. The optimal use of these drugs requires further study.

Immune-related adverse events commonly include pneumonitis, hepatitis, nephritis, colitis and endocrinopathies. However, nearly any organ system can be affected. These toxicities present clinicians with a new challenge of recognising them early and acting promptly.

Introduction

In the last 40 years, our understanding of the relationship between immune surveillance and tumour proliferation has advanced at a rapid pace. This has resulted in the development of immunotherapies such as the immune checkpoint inhibitors. Examples include ipilimumab, nivolumab, pembrolizumab, durvalumab and avelumab. These monoclonal antibodies are given by infusion.

Immune checkpoint inhibitors have already become the first-line treatment for patients with advanced melanoma and non-small cell lung cancer. Efficacy has also been shown in the second-line setting and there are ongoing phase III trials looking into their effectiveness in other cancer subtypes, such as lymphoma.¹

Mechanisms of action

One of the most fundamental characteristics of the human immune system is its ability to differentiate between self and non-self cells, such as tumour cells. This process is regulated by a balance between co-stimulatory and inhibitory signals, collectively known as immune checkpoints. Maintaining this balance is crucial for preventing an autoimmune reaction against normal cells.

T cells are lymphocytes involved in cell-mediated immune responses. T-cell activation begins when an antigen binds to a T-cell receptor.² This component of

the immune response is highly precise, as the receptor on the T cell is specific for one particular antigen. In addition to this antigen-specific binding, a 'second signal' is needed for T-cell activation. This involves co-stimulatory receptors such as CD28.

The two-step process acts as a fail-safe, to prevent an inappropriate immune response causing damage to healthy tissues. If a second signal is not received, the T cells become anergic.

Two pathways are central to the immune process:

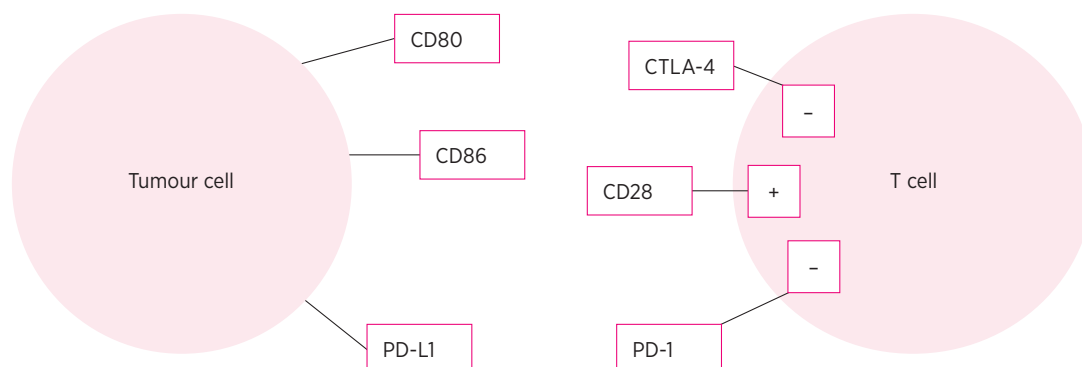
- cytotoxic T-lymphocyte associated antigen 4 (CTLA-4)
- programmed cell death 1 (PD-1) molecule.

The CTLA-4 pathway is the best studied and its predominant role is as an immune dampener to prevent the initial activation of T cells in lymph nodes. PD-1 regulates the interaction of already activated T cells in extra-lymphatic tissues (see Fig.).²

Highly mutant tumours are commonly able to acquire, or 'hijack' the immune checkpoints. This allows tumour cells to be inappropriately recognised as self tissues and so they restrain the T cell's ability to mount an effective antitumour response.

The immune checkpoint inhibitors stop the inhibitory effects of tumour cells on T cells. By inhibiting the immune checkpoints, immune-mediated antitumour activity is restored.

Fig. Immune checkpoints



CTLA-4 cytotoxic T-lymphocyte associated antigen 4
PD-1 programmed cell death 1
PD-L1 programmed cell death ligand 1
+ stimulatory pathway
- inhibitory pathway

Inhibiting the immune checkpoints reduces the body's ability to dampen the immune response. This causes a marked increase in immune-mediated toxicity and attacks on healthy tissues. It is this mechanism that accounts for the broad range of immune-related adverse events associated with immune checkpoint inhibitors.³

CTLA-4 pathway

The CTLA-4 receptor is part of an inhibitory pathway. This downregulates T-cell function and acts in conjunction with the co-stimulatory receptor CD28. The CTLA-4 molecule and CD28 are expressed on T cells. Both bind the ligands CD80 and CD86 which are located on the surface of antigen-presenting cells. CTLA-4 binds CD80/CD86 with a significantly greater affinity and avidity than CD28. This binding results in a CTLA-4 and CD80/CD86 complex which has an immune dampening effect and leads to T-cell anergy. Conversely, if a complex of CD28 with CD80/CD86 is formed, then a co-stimulatory signal is produced and T-cell activation occurs. The relative ratio of CD80/CD86 binding with CD28 versus CTLA-4 will determine whether a T cell will undergo activation or anergy.⁴

Tumour cells can generate inappropriate CTLA-4 signalling, enabling them to evade normal immune surveillance. Ipilimumab⁴ and tremelimumab are both fully human monoclonal antibodies that bind CTLA-4 and antagonise the binding of CTLA-4 with CD80/CD86. This then allows for increased binding of CD28 with CD80/CD86 leading to immune recognition of the tumour cells and T-cell activation.

PD-1 pathway

The PD-1 pathway has an inhibitory effect on the immune system. It downregulates T-cell function. The PD-1 molecule is expressed on T cells and binds to programmed cell death ligand 1 (PD-L1), which is found on antigen-presenting cells. This interaction between PD-1 and PD-L1 produces a signal that inhibits T-cell proliferation, resulting in immune dampening and T-cell anergy.⁵

Tumour cells can develop the ability to harness this mechanism resulting in inappropriate PD-L1 expression and activation of the inhibitory signalling pathway. This enables tumours to evade antigen-specific T-cell immune responses.

Nivolumab and pembrolizumab are both fully human monoclonal antibodies that inhibit the interaction between PD-1 and PD-L1. This prevents the downregulation of T cells and tumour cell evasion of normal immune surveillance.^{2,5} Recognition of the tumour cells enhances antitumour immune-mediated activity.

CTLA-4 inhibitors

Ipilimumab, a fully human monoclonal antibody, is a CTLA-4 inhibitor. By blocking the inhibitory effect of CTLA-4 on T cells, ipilimumab can stimulate a T-cell-mediated immune response against the cancer cells.⁶

Ipilimumab was approved after it was shown to prolong median overall survival from six months to 10 months in patients with advanced melanoma in a phase III randomised controlled trial.^{7,8} Before this, the median overall survival had ranged from

6–7 months with dacarbazine chemotherapy alone. However, when ipilimumab was later compared to more recently developed PD-1 immune checkpoint inhibitors, it was found to be inferior as a monotherapy.

Tremelimumab is another CTLA-4 inhibitor. In April 2008, a phase III trial in advanced melanoma was discontinued after a review of interim data indicated that tremelimumab was not superior to standard chemotherapy. The clinical role of tremelimumab has since remained limited.

PD-1 inhibitors

Programmed cell death ligand 1 (PD-L1) is expressed on the surface of multiple tissue types, including kidneys and lungs, and is important in normal immune function. PD-1 inhibitors prevent the ligand from binding to its receptor, thus allowing the immune system to recognise cancer cells.

Nivolumab has efficacy in the treatment of advanced melanoma, non-small cell lung cancer and renal cell carcinoma.⁹ Pembrolizumab has been used in the treatment of advanced melanoma, non-small cell lung cancer and advanced urothelial bladder cancer.

Durvalumab has efficacy in advanced urothelial bladder cancer and stage III non-small cell lung cancer. Avelumab has been approved for a rare skin cancer called Merkel cell carcinoma.

Melanoma

Ipilimumab was the first immune checkpoint inhibitor to show benefit in advanced melanoma. However, more recently other double-blind randomised controlled trials have shown the PD-1 inhibitors nivolumab and pembrolizumab to be more efficacious (see Table).^{9–11}

CheckMate 238

The CheckMate 238 study was a double-blind, phase III randomised controlled trial which directly compared ipilimumab with nivolumab as first-line therapy for advanced melanoma. This trial included patients aged over 15 years who had undergone complete surgical resection of either a stage IIIb, IIIc or IV melanoma.

The 12-month rate of recurrence-free survival was 70.5% in the nivolumab group and 60.8% in the ipilimumab group. Treatment-related adverse events were high in both groups and reported in 85.2% of the patients given nivolumab and 95.8% of patients given ipilimumab. Treatment was discontinued due to toxicities in 7.7% of the nivolumab group and 41.7% of the ipilimumab group.⁹ As a result of the significant toxicity with ipilimumab, the dose was reduced in subsequent studies, with the aim of reducing morbidity and treatment discontinuation rates.

CheckMate 067

The CheckMate 067 study was another double-blind, phase III trial which randomised patients in a 1:1:1 ratio to receive either ipilimumab, nivolumab or ipilimumab in combination with nivolumab, for untreated, unresectable advanced melanoma.

After a minimum follow-up of 36 months, the median overall survival had not been reached in the nivolumab plus ipilimumab group, but was 37.6 months with nivolumab and 19.9 months with ipilimumab monotherapy. The overall survival rate at three years was 58% with the combination therapy group compared with 52% in the nivolumab group and 34% in the ipilimumab group. This trial was not designed to detect a difference between

Table Phase III trials of immune checkpoint inhibitors in advanced melanoma

Trials (number of patients)	Treatment	Efficacy	Treatment-related adverse effects
CheckMate 238 ⁹ (906)	Ipilimumab (10 mg/kg every 3 weeks)	12-month progression-free survival	60.8%
	Nivolumab (3 mg/kg every 2 weeks)		70.5%
CheckMate 067 ¹⁰ (945)	Ipilimumab (3 mg/kg every 3 weeks)	24-month overall survival	45%
	Nivolumab (3 mg/kg every 2 weeks)		59%
	Nivolumab (1 mg/kg) + ipilimumab (3 mg/kg every 3 weeks), then nivolumab (3 mg/kg every 2 weeks)		64%
KEYNOTE-006 ¹¹ (834)	Ipilimumab (3 mg/kg every 3 weeks)	24-month overall survival	43%
	Pembrolizumab (10 mg/kg every 3 weeks)		55%
	Pembrolizumab (10 mg/kg every 2 weeks)		55%

the two nivolumab-containing groups, but did show significantly improved overall survival and progression-free survival with nivolumab, compared to ipilimumab monotherapy. Treatment-related adverse events occurred in 96% of the patients in the nivolumab plus ipilimumab group, 86% of the nivolumab group, and 86% of the ipilimumab group. Respectively, these adverse events led to the withdrawal of 39%, 12% and 16% of the patients.¹⁰

KEYNOTE-006

The KEYNOTE-006 study was a double-blind, phase III randomised controlled trial in patients with advanced melanoma. Patients were assigned in a 1:1:1 ratio to pembrolizumab every two weeks, pembrolizumab every three weeks or ipilimumab every three weeks.

The two pembrolizumab-containing groups showed higher six-month progression-free survival rates compared with the ipilimumab group (46.4% and 47.3% vs 26.5%). The respective 12-month overall survival rates were 74.1% and 68.4% versus 58.2%. There was no statistically significant difference detected between the two pembrolizumab-containing groups. The rates of immune-related adverse events of grade 3 to 5 (death) were lower in the pembrolizumab groups (13.3% and 10.1%) than in the ipilimumab group (19.9%).¹¹

Interpretation

In these trials the PD-1 inhibitors nivolumab and pembrolizumab significantly outperformed the CTLA-4 inhibitor ipilimumab as monotherapy for patients with advanced melanoma. Combining these therapies has yielded further positive results, but trials to date lack the statistical power to detect a significant difference between combination therapy and nivolumab or pembrolizumab monotherapy.

There are two key groups that benefit from combination therapy. These are firstly patients with BRAF mutation positive melanoma and, secondly, patients with brain metastases. Unfortunately, this benefit is often coupled with increased toxicity. Patients must be well informed regarding the toxicities of combination immunotherapy, balanced against any potential benefit. Patients with poor functional status or significant comorbidities may not be eligible for combination therapy.

In clinical practice, PD-1 inhibitor monotherapy is now well established as the first-line treatment in Australia for patients with the BRAF wild-type form of advanced melanoma. The use of ipilimumab and nivolumab in combination has now been approved by the Therapeutic Goods Administration (TGA) for patients with unresectable stage III or IV melanoma.

Non-small cell lung cancer

The KEYNOTE-024 study was an open label, phase III trial in 305 patients with previously untreated advanced non-small cell lung cancer, with more than 50% PD-L1 expression on biopsy. They were randomised to either pembrolizumab or the investigator's choice of platinum-based chemotherapy.

After a median follow-up of 11.2 months, the median progression-free survival was 10.3 months in the pembrolizumab group compared with six months in the chemotherapy group. The median overall survival at six months was 80.2% with pembrolizumab and 72.4% with chemotherapy. The response rate was also higher in the pembrolizumab group with the median duration of that response being significantly longer and associated with less immune-related adverse events than chemotherapy.¹²

The trial showed that pembrolizumab resulted in significantly longer progression-free survival, overall survival and fewer adverse events than with platinum-based chemotherapy. Pembrolizumab is now the first-line treatment for advanced non-small cell lung cancer in patients with PD-L1 expression higher than 50%. It can also be used in the second-line setting for patients with advanced non-small cell lung cancer who have been unable to tolerate or have progressed despite platinum-based chemotherapy.

Most patients with locally advanced or unresectable non-small cell lung cancer will experience disease progression despite combination chemo-radiotherapy. The PACIFIC trial randomised 713 patients with locally advanced or unresectable stage III non-small cell lung cancer whose disease had not progressed on combination platinum-based chemo-radiotherapy. It compared sequential treatment with the PD-L1 inhibitor durvalumab versus placebo.¹³

The median progression-free survival was 16.8 months with durvalumab versus 5.6 months with placebo. This effect was consistent across all patient subgroups analysed. There was slightly higher treatment-related toxicity seen in the durvalumab group (29% vs 26%), most commonly pneumonia, but severe toxicity was similar between groups.¹³ Durvalumab is now TGA-approved for use in Australia, but is not yet PBS-listed and is only available through a drug company access scheme.

Urothelial bladder carcinoma

The KEYNOTE-045 study was a phase III trial that studied 542 patients with advanced urothelial cancer that had recurred or progressed after platinum-based chemotherapy. They were randomised to receive either second-line pembrolizumab or the investigator's choice of chemotherapy with paclitaxel, docetaxel or vinflunine.

After a median follow-up of 14.1 months, the median overall survival was 10.3 months in the pembrolizumab group and 7.4 months in the chemotherapy group. The degree of PD-L1 expression did not appear to affect the outcome. Additionally, there were fewer treatment-related adverse events in the pembrolizumab group than in the chemotherapy group (60.9% vs 90.2%).¹⁴ Pembrolizumab is now TGA-approved for this indication, although it is not PBS-listed and is only available through a drug company access scheme.

Lymphoma

Studies have shown the PD-1 inhibitors nivolumab and pembrolizumab to be effective in the treatment of refractory or relapsed lymphoma. Their use has resulted in improved partial and complete responses and is evolving to become central in the treatment of lymphoma. Current studies are now assessing PD-1 inhibitors in combination with immunomodulatory therapies for lymphoma, as well as searching for predictive biomarkers.¹

Renal cell carcinoma

In advanced renal cell carcinoma, treatment options have until recently been limited to anti-angiogenic therapies. A randomised controlled trial compared nivolumab to everolimus, an inhibitor of the mTOR pathway and the current standard of care at the time. The median overall survival was 25 months with nivolumab compared with 19.6 months with everolimus. The progression-free survival was only marginally improved by 0.2 months with nivolumab (4.6 months vs 4.4 months). The treatment-related adverse events were lower in the nivolumab group at 19% compared with 37% in patients receiving everolimus.¹⁵ Nivolumab is now approved in Australia for the treatment of patients with advanced, clear cell renal cell carcinoma who have undergone previous treatment with an anti-angiogenic therapy.

Immunotherapy-related adverse events

The use of immune checkpoint inhibitors in clinical practice brings with it a spectrum of new toxicities. In addition to infusion reactions, there are immune-related adverse events that can affect almost any organ site. These include pneumonitis, hepatitis, nephritis, colitis and endocrinopathies. The new challenge for health professionals is recognising these toxicities early and acting promptly. In general, immune-related adverse events occur within two weeks to three months after the immune checkpoint inhibitor is given. However, immune-related adverse events have been reported as long as one year after discontinuation of treatment.

The most common toxicities are lethargy, rash with pruritus, liver toxicity, diarrhoea with colitis and hypophysitis. However, due to the broad range of possible toxicities, there should always be a low threshold for investigating any symptoms with radiological and biochemical tests. Although there are no clear guidelines on routine monitoring during treatment with an immune checkpoint inhibitor, in an otherwise asymptomatic patient it would be reasonable to check a full blood count, with kidney, liver and thyroid function every 2–4 weeks.

The mainstay of treatment for immune-related adverse reactions involves either dose reduction or cessation of the drug, and consideration of immunosuppression. Often with moderate toxicity, the immunotherapy drug can be temporarily withheld and resumed when symptoms have resolved. Additionally, a short course of oral prednisone (0.5 mg/kg) can be given if symptoms have not resolved within one week. For severe toxicities, the immunotherapy should be permanently discontinued and intravenous methylprednisolone (1–2 mg/kg/day) given. Once symptoms have improved, prednisone can be gradually weaned over the course of 1–2 months. In rare cases where prednisone is ineffective, infliximab, intravenous immunoglobulin and plasmapheresis may be required. The management for all immune-related toxicities is discussed in significantly greater detail in the ESMO clinical practice guidelines¹⁶ and eviQ.¹⁷

Duration of therapy

There is a very limited evidence base detailing the total duration of immune checkpoint inhibitor therapy. It is likely that the majority of patients are treated longer than necessary and a recent analysis¹⁸ has shown this, identifying that patients who discontinued treatment earlier due to toxicities achieved the same benefit as those who completed their planned treatment course. However, there is a paucity of high-quality trial data and the duration of treatment is left to the best judgement of the treating oncologists or departmental policies.

Conclusion

Immune checkpoint inhibitors can improve progression-free survival and overall survival in some patients with advanced malignancies. However, a significant proportion of patients do not respond and still have a poor prognosis. There are ongoing trials with novel immunotherapy combinations which aim to treat refractory disease and identify predictive biomarkers to select likely responders from non-

responders. There are also ongoing trials looking at the use of immunotherapy in the adjuvant setting, especially in melanoma.

It is likely that these drugs will become increasingly used in clinical practice, with many novel immunotherapies currently being developed and trialed. The benefits and sequelae of these

drugs are being more frequently seen so health professionals will need to be alert for the emerging burden of chronic cancer-related disease and the identification and management of treatment-related adverse effects. ◀

Conflict of interest: none declared

REFERENCES

1. Galanina N, Kline J, Bishop MR. Emerging role of checkpoint blockade therapy in lymphoma. *Ther Adv Hematol* 2017;8:81-90. <https://doi.org/10.1177/2040620716673787>
2. Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and anti-CTLA-4 therapies in cancer: mechanisms of action, efficacy, and limitations. *Front Oncol* 2018;8:86. <https://doi.org/10.3389/fonc.2018.00086>
3. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* 2018;378:158-68. <https://doi.org/10.1056/NEJMra1703481>
4. Camacho LH. CTLA-4 blockade with ipilimumab: biology, safety, efficacy, and future considerations. *Cancer Med* 2015;4:661-72. <https://doi.org/10.1002/cam4.371>
5. Alsaab HO, Sau S, Alzhrani R, Tatiparti K, Bhise K, Kashaw SK, et al. PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. *Front Pharmacol* 2017;8:561. <https://doi.org/10.3389/fphar.2017.00561>
6. Walker LS, Sansom DM. The emerging role of CTLA4 as a cell-extrinsic regulator of T cell responses. *Nat Rev Immunol* 2011;11:852-63. <https://doi.org/10.1038/nri3108>
7. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711-23. <https://doi.org/10.1056/NEJMoa1003466>
8. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011;364:2517-26. <https://doi.org/10.1056/NEJMoa1104621>
9. Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al.; CheckMate 238 Collaborators. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med* 2017;377:1824-35. <https://doi.org/10.1056/NEJMoa1709030>
10. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2017;377:1345-56. <https://doi.org/10.1056/NEJMoa1709684>
11. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al.; KEYNOTE-006 investigators. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med* 2015;372:2521-32. <https://doi.org/10.1056/NEJMoa1503093>
12. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al.; KEYNOTE-024 Investigators. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016;375:1823-33. <https://doi.org/10.1056/NEJMoa1606774>
13. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al.; PACIFIC Investigators. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017;377:1919-29. <https://doi.org/10.1056/NEJMoa1709937>
14. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al.; KEYNOTE-045 Investigators. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med* 2017;376:1015-26. <https://doi.org/10.1056/NEJMoa1613683>
15. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al.; CheckMate 025 Investigators. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015;373:1803-13. <https://doi.org/10.1056/NEJMoa1510665>
16. Haanen JB, Carbone F, Robert C, Kerr KM, Peters S, Larkin J, et al.; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017;28 suppl_4:iv119-42. <https://doi.org/10.1093/annonc/mdx225>
17. EviQ. Management of immune-related adverse events (irAEs) [Internet]. Sydney: Cancer Institute NSW; 2018. www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/immunological/1993-management-of-immune-related-adverse-events [cited 2019 Mar 1]
18. Schadendorf D, Wolchok JD, Hodi FS, Chiarion-Sileni V, Gonzalez R, Rutkowski P, et al. Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: a pooled analysis of randomized phase II and III trials. *J Clin Oncol* 2017;35:3807-14. <https://doi.org/10.1200/JCO.2017.73.2289>

New drugs

Aust Prescr 2019;42:68–9

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First published
28 February 2019

Bictegravir/emtricitabine/tenofovir alafenamide

Approved indication: HIV infection

Biktarvy (Gilead)

50 mg (with 200 mg and 25 mg) film-coated tablets

Australian Medicines Handbook section 5.6,

Antiretrovirals

The current approach to previously untreated patients with HIV infection is to prescribe a regimen of at least three antiretroviral drugs from two or more different classes. An integrase inhibitor, such as dolutegravir or elvitegravir, is usually included in these regimens.

The new product is a fixed-dose combination of bictegravir (an integrase inhibitor) with emtricitabine (a nucleoside reverse transcriptase inhibitor) and tenofovir alafenamide (a nucleotide analogue).

Like other integrase inhibitors, bictegravir blocks the integration of viral DNA into cellular DNA. This step is essential for viral replication.

The combination product is taken once a day. The bictegravir component has a half-life of 17 hours and it is mainly cleared by metabolism. As this pathway includes cytochrome P450 3A there is a potential for interaction with other drugs metabolised by this enzyme. Co-administration with rifampicin is contraindicated. As the product also contains emtricitabine and tenofovir, there are many potential drug interactions. The combination is not recommended if the patient's creatinine clearance is below 30 mL/min. It has not been studied in severe liver impairment.

There have been two main trials of the combination in untreated patients. These were non-inferiority studies comparing the combination with other three-drug regimens.

In one of these trials the comparative regimen also included emtricitabine and tenofovir alafenamide, but used dolutegravir for integrase inhibition. This trial randomised 657 patients who had at least 500 copies of viral RNA/mL of plasma. They were to be treated for 144 weeks, but the response to therapy was assessed at 48 weeks. At this time point, viral RNA concentrations were below 50 copies/mL for 89.4% of the patients taking the bictegravir combination and for 92.9% of those taking the comparison regimen.¹

The other trial compared the combination with a regimen containing dolutegravir, abacavir and lamivudine. In this trial 631 patients, with viral RNA

of at least 500 copies/mL, were randomised to 144 weeks of treatment. After 48 weeks the viral RNA was below 50 copies/mL in 92.4% of the patients taking the combination and 93% of those taking the other regimen.²

Having established that the combination is non-inferior to other regimens for initial treatment, there has been research into switching patients, taking other regimens, to the new combination. These patients already had viral RNA below 50 copies/mL. One study of 567 patients taking dolutegravir, abacavir and lamivudine switched 284 of them to the new combination. After 48 weeks viral RNA remained below 50 copies/mL in 94% of those who switched and in 95% of those who did not.³

An open-label study assessed the combination in 578 patients treated with regimens containing a protease inhibitor. There were 290 patients who switched to the combination and after 48 weeks the virus remained suppressed in 92% compared with 89% of the patients who did not switch treatment.⁴

Few patients had to discontinue treatment because of adverse events. In one of the studies of previously untreated patients 2% withdrew,¹ while in the other study there were no withdrawals.² Treatment-related events were less frequent with bictegravir than they were with a similar regimen using dolutegravir (18% vs 26%).¹ Common adverse events include headache, diarrhoea and nausea. In one of the switching studies treatment-related adverse events were more frequent in the patients who changed to the bictegravir product (19% vs 2%). The main differences were in the frequency of headache, flatulence and diarrhoea.⁴ Although the combination can increase serum creatinine and bilirubin, no patients had to stop treatment because of renal or hepatic adverse effects. There is limited information about the safety of the combination in patients co-infected with hepatitis B. There is a possibility that the hepatitis may flare up if treatment with the combination is stopped. The safety in pregnancy is uncertain as women who became pregnant in the trials stopped the combination.^{1–3} There was no evidence of teratogenicity in animal studies.

Adhering to treatment is vital in the management of HIV infection. A single daily tablet should help to achieve and maintain viral suppression. There were no cases of treatment-emergent resistance during the trials.^{1–4}

T manufacturer provided the product information



Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

REFERENCES

1. Sax PE, Pozniak A, Montes ML, Koenig E, DeJesus E, Stellbrink HJ, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet* 2017;390:2073-82. [https://doi.org/10.1016/S0140-6736\(17\)32340-1](https://doi.org/10.1016/S0140-6736(17)32340-1)
2. Gallant J, Lazzarin A, Mills A, Orkin C, Podzamczar D, Tebas P, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet* 2017;390:2063-72. [https://doi.org/10.1016/S0140-6736\(17\)32299-7](https://doi.org/10.1016/S0140-6736(17)32299-7)
3. Molina JM, Ward D, Brar I, Mills A, Stellbrink HJ, López-Cortés L, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet HIV* 2018;5:e357-65. [https://doi.org/10.1016/S2352-3018\(18\)30092-4](https://doi.org/10.1016/S2352-3018(18)30092-4)
4. Daar ES, DeJesus E, Ruane P, Crofoot G, Oguchi G, Creticos C, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. *Lancet HIV* 2018;5:e347-56. [https://doi.org/10.1016/S2352-3018\(18\)30091-2](https://doi.org/10.1016/S2352-3018(18)30091-2)

The Transparency Score is explained in [New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.](#)

At the time the comment was prepared, information about this drug was available on the websites of the [Food and Drug Administration in the USA](#), the [European Medicines Agency](#) and the [Therapeutic Goods Administration](#).

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Ertugliflozin

Approved indication: type 2 diabetes

Steglatro (Merck Sharp & Dohme)

5 mg or 15 mg film-coated tablets

Segluromet (Merck Sharp & Dohme)

2.5 mg ertugliflozin/500 mg metformin,

2.5 mg ertugliflozin/1000 mg metformin,

7.5 mg ertugliflozin/500 mg metformin,

7.5 mg ertugliflozin/1000 mg metformin

Steglujan (Merck Sharp & Dohme)

5 mg ertugliflozin/100 mg sitagliptin,

15 mg ertugliflozin/100 mg sitagliptin

Australian Medicines Handbook section 10.1.5, Sodium-glucose co-transporter 2 inhibitors

Ertugliflozin is another sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated for type 2 diabetes. It can be used as a monotherapy (as an alternative when metformin is not appropriate) or in combination with other drugs for diabetes, in conjunction with diet and exercise.

Like other SGLT2 inhibitors canagliflozin, dapagliflozin and empagliflozin, ertugliflozin reduces blood glucose by decreasing the renal reabsorption of glucose and increasing its excretion. Because glucose is lost in the urine, these drugs are also associated with weight loss.

The approval of ertugliflozin is based on seven randomised placebo or active comparator phase III trials (see Table).^{1–8} In total, 4863 adults (mean age 58 years) with inadequately controlled type 2 diabetes were included. The main outcome in the trials was change in glycated haemoglobin (HbA1c). Body weight was also measured.

In a monotherapy trial (VERTIS MONO), patients were randomised to daily ertugliflozin (5 mg or 15 mg) or placebo. After 26 weeks of treatment, mean HbA1c had dropped with ertugliflozin but increased with placebo. This difference was statistically significant ($p=0.001$).¹ These lower HbA1c concentrations were maintained through to 52 weeks with ertugliflozin.² Decreases in HbA1c were also seen in a second trial (VERTIS SITA) in which ertugliflozin (5 mg or 15 mg) was given as initial therapy in combination with sitagliptin 100 mg (see Table).³

Reduction in HbA1c was observed when ertugliflozin was added to the treatment of patients whose blood glucose was inadequately controlled with metformin (VERTIS MET⁴ and VERTIS SU⁵ trials). In the VERTIS SU trial, adding ertugliflozin 15 mg was found to be non-inferior to adding glimepiride.⁵

In the VERTIS FACTORIAL trial HbA1c reductions were observed when ertugliflozin and sitagliptin were added to metformin.⁶ Similar results were observed in the VERTIS SITA2 trial when ertugliflozin was given to patients already taking a combination of metformin and sitagliptin.⁷ This effect was maintained to week 52 in both trials. Ertugliflozin consistently reduced body weight in the VERTIS trials.^{1–7}

Ertugliflozin added to usual therapy has also been investigated in people with stage 3 chronic kidney disease (estimated glomerular filtration rate of ≥ 30 to < 60 mL/min/1.73 m²) in the VERTIS RENAL trial.⁸ However, after 26 weeks of treatment, ertugliflozin was not more effective at lowering HbA1c than placebo (see Table).

The most common adverse events with ertugliflozin in the trials included genital mycotic infections (9–12% of women, 4% of men), increased urination (2.5%), vulvovaginal pruritis (1%) and increased thirst (1%). As with other SGLT2 inhibitors, ertugliflozin can cause volume depletion, particularly in those with an eGFR of less than 60 mL/min/1.73 m². Monitoring volume status and electrolytes is recommended if there is a risk of fluid loss such as diarrhoea, heat stress or severe infection. Patients may become hypotensive with ertugliflozin.

Ketoacidosis has been reported with this drug so patients should be assessed for risk factors before starting treatment (e.g. low-carbohydrate diet, dehydration, acute illness, insulin dose reduction, alcohol misuse).

Ertugliflozin was associated with increases in serum creatinine and decreases in eGFR. These changes were greater in people with impaired renal function but were reversible when the drug was stopped. Renal function should therefore be monitored before and during ertugliflozin and when concomitant drugs that may affect renal function are used. Ertugliflozin is contraindicated in patients on dialysis, and in those with an eGFR of less than 30 mL/min/1.73 m² or persistently less than 45 mL/min/1.73 m².

Lower limb amputations were more common in people receiving ertugliflozin (0.47% with 5 mg dose, 0.26% with 15 mg dose) than those who did not receive it (0.07%). This has previously been found with canagliflozin which is no longer registered for use in Australia.

There have been no clinical studies of ertugliflozin in pregnancy or lactation. However in animal studies, the drug crossed the placenta and was excreted in the milk of lactating rats. At high doses, fetal viability was reduced and cardiac malformations

Table Efficacy of ertugliflozin in clinical trials

Study (duration, participants, mean baseline HbA1c)	Daily treatment	Trial outcomes*	
		Change in HbA1c	Body weight (kg)
Monotherapy			
VERTIS MONO ¹ (26 weeks, 461 patients, baseline HbA1c 8.2%)	ertugliflozin 5 mg	−0.8%	−3.2
	ertugliflozin 15 mg	−1.0%	−3.6
	placebo*	+0.2%	−1.4
Initial combination therapy			
VERTIS SITA ³ (26 weeks, 291 patients, baseline HbA1c 8.9%)	ertugliflozin 5 mg + sitagliptin 100 mg	−1.6%	−2.9
	ertugliflozin 15 mg + sitagliptin 100 mg	−1.7%	−3.0
	placebo	−0.4%	−0.9
Add-on therapy to metformin ≥1500 mg			
VERTIS MET ⁴ (26 weeks, 621 patients, baseline HbA1c 8.1%)	ertugliflozin 5 mg	−0.7%	−3.0
	ertugliflozin 15 mg	−0.9%	−2.9
	placebo	0%	−1.3
Add-on therapy to metformin ≥1500 mg			
VERTIS SU ⁵ (52 weeks, 1326 patients, baseline HbA1c 7.8%)	ertugliflozin 5 mg	−0.6%	−3.0
	ertugliflozin 15 mg	−0.6%	−3.4
	glimepiride 6 or 8 mg	−0.7%	+0.9
Add-on combination therapy to metformin ≥1500 mg			
VERTIS FACTORIAL ⁶ (26 weeks, 1233 patients, baseline HbA1c 8.5–8.6%)	ertugliflozin 5 mg + sitagliptin 100 mg	−1.5%	−2.5
	ertugliflozin 15 mg + sitagliptin 100 mg	−1.5%	−2.9
	ertugliflozin 5 mg	−1.0%	−2.7
	ertugliflozin 15 mg	−1.1%	−3.7
	sitagliptin 100 mg	−1.1%	−0.7
Add-on therapy to metformin and sitagliptin ≥1500 mg			
VERTIS SITA2 ⁷ (26 weeks, 464 patients, baseline HbA1c 8%)	ertugliflozin 5 mg	−0.8%	−3.4
	ertugliflozin 15 mg	−0.9%	−3.0
	placebo	−0.1%	−1.3
Add-on therapy in stage 3 chronic kidney disease [†]			
VERTIS RENAL ⁸ (26 weeks, 468 patients, baseline HbA1c 8.2%)	ertugliflozin 5 mg	−0.3%	−1.3
	ertugliflozin 15 mg	−0.4%	−1.4
	placebo	−0.3%	+0.5

HbA1c glycated haemoglobin

* least squares mean change from baseline

† Ertugliflozin was added to usual diabetes therapy (e.g. insulin and sulfonylureas), however metformin, rosiglitazone and other SGLT2 inhibitors were not allowed.

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were increased. Ertugliflozin also affected kidney development when given to juvenile rats.

After once-daily oral administration, ertugliflozin is rapidly absorbed and steady state is reached within 4–6 days. Ertugliflozin is metabolised by UGT1A9- and UGT2B7-mediated O-glucuronidation. Its elimination half-life is 16.6 hours and it is excreted in the faeces (41%) and urine (50%). Drug–drug interactions are not expected with ertugliflozin. However, concomitant insulin or an insulin secretagogue can increase the risk of hypoglycaemia and lower insulin doses may be required.

Ertugliflozin has similar efficacy and safety in type 2 diabetes to other SGLT2 inhibitors, although comparative trials have not been carried out. In the VERTIS trials, it reduced HbA1c when used on its own or in combination with metformin and sitagliptin. Its efficacy is dependent on renal function, and people with moderate renal impairment did not benefit in the trials.

T T manufacturer provided additional useful information

The Transparency Score is explained in *New drugs: transparency*, Vol 37 No 1, *Aust Prescr* 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency and the Therapeutic Goods Administration.

REFERENCES

1. Terra SG, Focht K, Davies M, Frias J, Derosa G, Darekar A, et al. Phase III, efficacy and safety study of ertugliflozin monotherapy in people with type 2 diabetes mellitus inadequately controlled with diet and exercise alone. *Diabetes Obes Metab* 2017;19:721-8. <https://doi.org/10.1111/dom.12888>
2. Aronson R, Frias J, Goldman A, Darekar A, Lauring B, Terra SG. Long-term efficacy and safety of ertugliflozin monotherapy in patients with inadequately controlled T2DM despite diet and exercise: VERTIS MONO extension study. *Diabetes Obes Metab* 2018;20:1453-60. <https://doi.org/10.1111/dom.13251>
3. Miller S, Krumins T, Zhou H, Huyck S, Johnson J, Golm G, et al. Ertugliflozin and sitagliptin co-initiation in patients with type 2 diabetes: the VERTIS SITA randomized study. *Diabetes Ther* 2018;9:253-68. <https://doi.org/10.1007/s13300-017-0358-0>
4. Gallo S, Charbonnel B, Goldman A, Shi H, Huyck S, Darekar A, et al. Long-term efficacy and safety of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: 104-week VERTIS MET trial. *Diabetes Obes Metab* 2019 Jan 7 [Epub ahead of print] <https://doi.org/10.1111/dom.13631>
5. Hollander P, Liu J, Hill J, Johnson J, Jiang ZW, Golm G, et al. Ertugliflozin compared with glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin: the VERTIS SU randomized study. *Diabetes Ther* 2018;9:193-207. <https://doi.org/10.1007/s13300-017-0354-4>
6. Pratley RE, Eldor R, Raji A, Golm G, Huyck SB, Qiu Y, et al. Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: the VERTIS FACTORIAL randomized trial. *Diabetes Obes Metab* 2018;20:1111-20. <https://doi.org/10.1111/dom.13194>
7. Dagogo-Jack S, Liu J, Eldor R, Amorin G, Johnson J, Hille D, et al. Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin: the VERTIS SITA2 placebo-controlled randomized study. *Diabetes Obes Metab* 2018;20:530-40. <https://doi.org/10.1111/dom.13116>
8. Grunberger G, Camp S, Johnson J, Huyck S, Terra SG, Mancuso JP, et al. Ertugliflozin in patients with stage 3 chronic kidney disease and type 2 diabetes mellitus: the VERTIS RENAL randomized study. *Diabetes Ther* 2018;9:49-66. <https://doi.org/10.1007/s13300-017-0337-5>

Midostaurin

Approved indications: acute myeloid leukaemia, mastocytosis, mast cell leukaemia

Rydapt (Novartis)

25 mg capsules

Australian Medicines Handbook section 14.2.4, Tyrosine kinase inhibitors

Tyrosine kinases play a role in certain haematological malignancies. In about 30% of cases of acute myeloid leukaemia there is a mutation of the gene which encodes for FMS-like tyrosine kinase 3 (FLT3). A mutation in another gene (KIT) which encodes tyrosine kinase is found in most cases of systemic mastocytosis. In this rare and potentially fatal condition there is a proliferation of mast cells which can accumulate in organs and bone marrow. Its most aggressive form is mast cell leukaemia.

Midostaurin is an inhibitor of several tyrosine kinases,¹ including those related to FLT3 and KIT. It induces apoptosis in leukaemic cells and inhibits mast cell proliferation.

The capsules are taken twice daily with food to reduce nausea. Midostaurin is metabolised by cytochrome P450 (CYP) 3A4 to form active metabolites. While midostaurin has a half-life of 20 hours, one of its metabolites has a half-life of 495 hours. Most of the dose is excreted in the faeces. Midostaurin and its metabolites may induce or inhibit the metabolism of other drugs and vice versa. Strong inducers of CYP3A4, such as carbamazepine, should be avoided as they decrease the concentrations of midostaurin. No dose adjustments are recommended for patients with mild-moderate liver or kidney impairment.

The main placebo-controlled trial of midostaurin in acute myeloid leukaemia involved 717 patients with the FLT3 mutation. They were randomised to receive chemotherapy with daunorubicin and cytarabine plus midostaurin (50 mg twice daily) or placebo. After an induction and consolidation phase patients who were in remission continued midostaurin or placebo for up to twelve 28-day cycles. This full course of treatment was completed by 69 of the 360 patients taking midostaurin and 51 of the 357 in the placebo group. From the time of randomisation, the median overall survival was 74.7 months with midostaurin and 25.6 months with placebo.²

A small study has followed up patients with advanced systemic mastocytosis for more than 10 years (median duration of follow-up 124 months). The 26 patients had been treated with midostaurin 100 mg twice daily for up to 12 cycles of 28 days, and 18 had responded. The patients who responded could

continue treatment. Their median overall survival was 41.2 months (19.2 months for non-responders).³

Another open-label trial in advanced systemic mastocytosis studied the same dose of midostaurin. There were 116 patients in the trial including 89 with organ damage due to mastocytosis and 16 with mast cell leukaemia. They were treated continuously in four-week cycles. The median duration of treatment was 11.4 months. There was a response in 60% of the patients which lasted for a median of 24.1 months. Responses included improvement in anaemia, thrombocytopenia and liver function. For example, eight of the 20 patients who had been dependent on red-cell transfusions were no longer dependent on them. The median overall survival was 33.9 months. In patients with organ damage it was 28.7 months and in those patients with mast cell leukaemia it was 9.4 months.⁴

The adverse effects of midostaurin are similar in acute myeloid leukaemia and systemic mastocytosis, but the frequencies are different. Febrile neutropenia affects 83.4% of patients with leukaemia, but only 7.7% of those with mastocytosis. Some of this difference may be due to the use of chemotherapy. Severe neutropenia is an indication to interrupt treatment. There were some deaths from cardiac dysfunction in patients with systemic mastocytosis, but there was no difference from the placebo group in myeloid leukaemia. Pulmonary toxicity has been reported with midostaurin monotherapy and in combination with chemotherapy. Adverse events led to midostaurin being stopped by 9.2% of the patients with leukaemia and 23.9% of those with mastocytosis. For both conditions very common adverse effects include infections, nausea, vomiting, headache, epistaxis and hyperglycaemia.

The three studies show the beneficial effects of midostaurin, but there are some questions. Acute myeloid leukaemia usually presents in older people, but the trial only included patients up to 59 years old. As 57% of the patients in this trial had an allogeneic transplant, and therefore stopped midostaurin, its benefit is less clear.² There is also some uncertainty in advanced systemic mastocytosis as the open-label studies were uncontrolled, however this is a rare disease with few treatment options.⁴

T [manufacturer provided the product information](#)

REFERENCES

1. Clarke SJ, Sharma R. Angiogenesis inhibitors in cancer – mechanisms of action. *Aust Prescr* 2006;29:9-12. <https://doi.org/10.18773/austprescr.2006.007>
2. Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med* 2017;377:454-64. <https://doi.org/10.1056/NEJMoa1614359>

Aust Prescr 2019;42:73-4
<https://doi.org/10.18773/austprescr.2019.017>

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NEW DRUGS

3. DeAngelo DJ, George TI, Linder A, Langford C, Perkins C, Ma J, et al. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. *Leukemia* 2018;32:470-8. <https://doi.org/10.1038/leu.2017.234>
4. Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. *N Engl J Med* 2016;374:2530-41. <https://doi.org/10.1056/NEJMoa1513098>

The Transparency Score is explained in *New drugs: transparency*, Vol 37 No 1, *Aust Prescr* 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

Nusinersen

Approved indication: spinal muscular atrophy

Spinraza (Biogen)

single-dose vials containing 12 mg/5 mL solution for injection

Australian Medicines Handbook Appendix A

Nusinersen is an orphan drug approved for the treatment of 5q spinal muscular atrophy. This is a rare genetic disease (approximately 1 in 10,000 births) which presents as progressive muscle weakness and atrophy. Until now, there have been no treatments for this disease.

Spinal muscular atrophy is classified into four types depending on age of onset and motor function:

- type 1 – onset 0–6 months, life expectancy less than 2 years
- type 2 – onset 6–18 months, life expectancy 10–40 years
- type 3 – onset after 18 months, life expectancy adulthood
- type 4 – onset after 5 years, life expectancy adulthood.

Approximately half of patients that present are babies with type 1 disease.

Patients with spinal muscular atrophy have insufficient levels of the survival motor neuron (SMN) protein which is essential for the survival and functioning of motor neurons. This protein is encoded by two genes – SMN1 and SMN2. In spinal muscular atrophy the SMN1 gene is lacking but SMN2 is present so patients produce a truncated form of the protein. Having fewer copies of the SMN2 gene is generally associated with earlier onset of disease and more severe symptoms. Nusinersen is a synthetic antisense oligonucleotide which works by enabling the SMN2 gene to produce a full length SMN protein.

Nusinersen 12 mg is administered by lumbar puncture. It should be given at 0, 2, 4 and 9 weeks followed by a maintenance dose every four months. The drug's terminal half-life in the cerebrospinal fluid is 19–25 weeks and it is mainly excreted in the urine. Nusinersen is metabolised by exonucleases, and drug interactions with the cytochrome P450 system have not been found.

The approval of nusinersen is based on several trials in patients aged from 30 days to 15 years. In babies, motor milestones were measured using scales such as the Hammersmith Infant Neurological Examination (HINE) which included evaluation of kicking, head control, rolling, sitting, crawling, standing and walking. The Hammersmith Functional Motor Scale-Expanded

(HFMSE) score was used to assess older children. This scale ranges from 1 to 66 with higher scores indicating better motor function.

A phase III randomised, placebo-controlled trial (ENDEAR) included 121 babies aged seven months or younger with type 1 disease. At baseline, all of them were hypotonic and most had delayed motor function development and limb weakness. After six injections of nusinersen or a placebo (0, 2, 4, 9 weeks then 6 and 10 months), half of those given nusinersen (37/73) had achieved motor milestones compared with none (0/37) of those given a sham injection. In the nusinersen group, 22% of babies developed full head control, 10% could roll over, 8% could sit unaided and 1% were able to stand. At the final analysis, 16% of the babies treated with nusinersen had died compared with 39% treated with a sham injection. A lower proportion of babies who received nusinersen had died or required permanent ventilation compared with those in the control group (39% vs 68%).¹ Improvements in motor milestones were also observed in an uncontrolled phase II trial (20 babies) with open-label 6–12 mg and 12 mg doses of nusinersen.²

A second randomised, controlled phase III trial (CHERISH) enrolled 126 children with later-onset disease whose symptoms started after six months of age (type 2 and 3 disease). At baseline, they had a median age of 3–4 years. All of them were able to sit, some could walk with support, but none could walk independently. After 15 months (treatment given at 0, 1, 3 and 10 months), children in the nusinersen group (n=84) had improved by 4 points on the HFMSE scale whereas those in the sham-injection group (n=42) had got worse by 1.9 points. (A change of at least 3 points on this 66-point scale is considered to be clinically meaningful.) The proportion of children who were able to stand independently at 15 months was no different with nusinersen than with the sham injection (1/84 vs 1/42).³

Adverse events were similar between the treatment and the control arms. The most common events with nusinersen were fever, constipation, rash, respiratory tract infection, pneumonia, nasopharyngitis and bronchiolitis. Reactions associated with lumbar puncture, like headache, back pain, vomiting and post-lumbar puncture syndrome, were also reported.

Thrombocytopenia, coagulation abnormalities and renal toxicity have occurred with other antisense oligonucleotides. Decreased platelet counts and elevated urine protein have been observed in some patients treated with nusinersen so blood and urine testing may be needed before or during treatment.

Nusinersen is the first treatment to be approved for spinal muscular atrophy in Australia. It seems to

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improve motor function in babies and children, but it is not yet known if the benefits will be sustained in the longer term and increase survival. Patients who completed the ENDEAR and CHERISH trials have been enrolled in an extension study (SHINE trial) which is planned to continue until 2023 and results have not yet been reported.

T T manufacturer provided additional useful information

REFERENCES

1. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Eng J Med* 2017;377:1723-32. <https://doi.org/10.1056/NEJMoa1702752>
2. Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet* 2016;388:3017-26. [https://doi.org/10.1016/S0140-6736\(16\)31408-8](https://doi.org/10.1016/S0140-6736(16)31408-8)
3. Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med* 2018;378:625-35. <https://doi.org/10.1056/NEJMoa1710504>

The Transparency Score is explained in [New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.](#)

At the time the comment was prepared, information about this drug was available on the websites of the [Food and Drug Administration](#) in the USA, and the [European Medicines Agency](#) and the [Therapeutic Goods Administration](#).

Pralatrexate

Approved indication: lymphoma

Folotyn (Mundipharma)

vials containing 20 mg/mL

**Australian Medicines Handbook section 14.1.3,
Antimetabolites**

One of the less frequent forms of lymphoma is peripheral T-cell lymphoma. Patients often present with advanced disease and have a poor prognosis even after stem-cell transplantation. As the cancer may be resistant to chemotherapy, there is a need for new treatments.

Pralatrexate is an analogue of the antifolate drug methotrexate. It inhibits the enzyme dihydrofolate reductase. The resulting depletion of folate disrupts DNA synthesis leading to the death of tumour cells.

Unlike methotrexate, pralatrexate has to be given by intravenous infusion over 3–5 minutes. The drug has a half-life of 12–18 hours with 31% being excreted unchanged in the urine. There is uncertainty about how the rest of a dose is eliminated, but pralatrexate is not thought to be metabolised by the cytochrome P450 system. Renal and hepatic function should be monitored during treatment. Caution is advised if the estimated glomerular filtration rate is below 60 mL/min and pralatrexate should not be used in patients with end-stage kidney disease.

Clinical trial data are limited. The main trial was open-label, non-randomised and uncontrolled. This trial enrolled 115 patients with peripheral T-cell lymphoma that had progressed despite at least one previous treatment. They were given weekly infusions for six weeks followed by one week of rest before the cycle was repeated. The median duration of treatment was 70 days. Based on clinical findings and imaging, the overall response rate (in 109 evaluable patients) was 29%. Only 11% achieved a complete response. Progression-free survival was 3.5 months with an overall survival of 14.5 months.¹

Antifolate drugs can cause frequent and serious adverse effects. In the trial 23% of the patients stopped treatment because of adverse effects, others had to reduce their dose. Common adverse effects included mucositis, altered liver function, thrombocytopenia, anaemia, fever, neutropenia and epistaxis.¹ Full blood counts should be measured weekly. There is a potential for serious skin reactions which may be fatal.

Although some patients will respond to pralatrexate, its efficacy is uncertain as it was not directly compared with any other treatment or placebo. The outcomes may be better, but come with the risk of potentially fatal toxicity. There is a need to research whether pralatrexate could be combined with other drugs. At present its indication is limited to treating patients with peripheral T-cell lymphoma after other therapy has failed.

TT [manufacturer provided additional useful information](#)

REFERENCES

1. O'Connor OA, Pro B, Pinter-Brown L, Bartlett N, Popplewell L, Coiffier B, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *J Clin Oncol* 2011;29:1182-9. <https://doi.org/10.1200/JCO.2010.29.9024>

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Safinamide

Approved indication: Parkinson's disease

Xadago (Seqirus)

50 mg and 100 mg tablets

Australian Medicines Handbook section 16.2.3, Monoamine oxidase type B inhibitors

In idiopathic Parkinson's disease there is a deficiency of dopamine. Treatment therefore involves taking levodopa, a dopamine agonist or both. Usually levodopa is formulated with a dopa decarboxylase inhibitor to reduce peripheral dopaminergic adverse effects. As the disease progresses, long-term use of levodopa is associated with its effect wearing off between doses. To manage the resultant motor fluctuations, additional therapy may be considered. The options include inhibitors of monoamine oxidase type B. Inhibiting this enzyme reduces dopamine metabolism and so increases dopamine concentrations in the brain.

Safinamide is a selective, reversible monoamine oxidase type B inhibitor. It also inhibits the release of glutamate, a substance which may have a role in the motor fluctuations. The drug is well absorbed and has a half-life of 20–30 hours. It is suitable for once-daily dosing with or without food. Most of the dose is metabolised with the metabolites being mainly excreted in the urine. Lower doses are recommended for patients with moderate liver impairment, but safinamide is contraindicated in severe impairment.

The main clinical trials of safinamide have studied patients who were having motor fluctuations despite treatment with levodopa. One trial randomised 549 patients to add safinamide (target dose 100 mg daily) or a placebo to their treatment. The primary outcome was the change in the duration of the relief from motor symptoms ('on time') without troublesome dyskinesia. At the start of the study the daily on time was 9.3 hours in the safinamide group and 9.06 hours in the placebo group. After 24 weeks the on time increased by 1.42 hours with safinamide and 0.57 hours with placebo. Based on a clinical global impression, 57.7% of the patients taking safinamide improved compared with 41.8% of those taking a placebo.¹

Another placebo-controlled trial randomised 669 patients to take safinamide 50 mg or 100 mg daily for 24 weeks. From a baseline of approximately 9.4 hours, the on time, without troublesome dyskinesia, increased by 1.37 hours with safinamide 50 mg and by 1.36 hours with 100 mg. The increase in the placebo group was 0.97 hours. The respective proportions of patients judged to have a clinical global improvement were 66.4%, 64.3%

and 55.4%.² Patients who completed this trial could continue in an extension study.

There were 544 patients in the extension study. They continued in their original randomised groups for up to two years. The primary outcome was the change in the Dyskinesia Rating Scale from baseline to 24 months. This improved by 31% in patients taking safinamide 50 mg and by 27% in those taking 100 mg. There was only a 3% change in the placebo group. At the end of the study the on time without dyskinesia had increased by 1.01 hours with 50 mg, 1.18 hours with 100 mg and by 0.34 hours with placebo.³

Drugs that increase concentrations of dopamine can be expected to have adverse effects such as insomnia and altered blood pressure. In the clinical trials of safinamide the most frequent adverse events were dyskinesia, falls, nausea and insomnia. In the two-year study 6.7% of the patients stopped taking 100 mg safinamide because of adverse events. The withdrawal rate with 50 mg was similar to that of placebo (5.3 vs 5.7%).³

Although safinamide is selective for monoamine oxidase type B and dietary tyramine restrictions are not required, these are potentially serious drug interactions. Co-administration with pethidine is contraindicated and there is a risk of serotonin syndrome with other opioids and antidepressants. If the patient has been taking a serotonergic drug, a washout of at least five times the half-life is recommended before starting safinamide. To avoid potential interactions, doses of drugs such as ciprofloxacin, diclofenac and pravastatin should be separated from doses of safinamide by at least five hours.

Retinal degeneration was reported in some animal studies. Safinamide is therefore contraindicated in patients with conditions such as uveitis and retinopathy.

Safinamide adds another monoamine oxidase B inhibitor for managing fluctuating idiopathic Parkinson's disease. It increases on time more than a placebo does. Whether it has any advantage over other monoamine oxidase type B inhibitors is unknown. The longer-term effectiveness of safinamide also requires further scrutiny. During the two-year study the reduction in dyskinesia was greater than with placebo but was not statistically significant.³ In a 12-month extension of a trial studying safinamide in early-stage Parkinson's disease, there was no difference from placebo in delaying the need to intensify treatment.⁴ Whether these observations reflect declining efficacy or the progression of the disease is unclear.

T T manufacturer provided additional useful information

REFERENCES

1. Schapira AH, Fox SH, Hauser RA, Jankovic J, Jost WH, Kenney C, et al. Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. *JAMA Neurol* 2017;74:216-24. <https://doi.org/10.1001/jamaneurol.2016.4467>
2. Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt M, Chirilineau D, et al. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. *Mov Disord* 2014;29:229-37. <https://doi.org/10.1002/mds.25751>
3. Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt MH, Chirilineau D, et al. Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. *Mov Disord* 2014;29:1273-80. <https://doi.org/10.1002/mds.25961>
4. Schapira AH, Stocchi F, Borgohain R, Onofri M, Bhatt M, Lorenzana P, et al. Long-term efficacy and safety of safinamide as add-on therapy in early Parkinson's disease. *Eur J Neurol* 2013;20:271-80. <https://doi.org/10.1111/j.1468-1331.2012.03840.x>

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A:

ANSWERS TO SELF-TEST QUESTIONS

1 True 2 False

Correction

The hot patient: acute drug-induced hyperthermia [Correction]

Aust Prescr 2019;42:79

<https://doi.org/10.18773/austprescr.2019.022>

First published 18 February 2019

A formatting error in the article by Nazila Jamshidi and Andrew Dawson has been corrected.

[View corrected article.](#)

The diaphoresis row in Table 3 (Clinical features of neuroleptic malignant syndrome, serotonin toxicity, anticholinergic syndrome and sympathomimetic syndrome) was incorrect. Diaphoresis in serotonin toxicity is moderate (not severe), it is not a feature of anticholinergic toxicity (not moderate), and it is moderate (not severe) in sympathomimetic syndrome.

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