This third article in the series on antidepressants reviews the monoamine-oxidase inhibitors (MAOIs). A chance discovery by chest clinicians led to the development of this class of antidepressant medications. Although MAOIs are not the first choice in modern-day drug therapy due to significant side-effects and drug interactions, they have played an important role in the development of the pharmaceutical management of depression. Focusing on moclobemide for clarity, this article discusses the pharmacokinetics and pharmacodynamics of this class of drugs, before discussing precautions and prescribing in special populations. A summary of MAOIs currently in use and their alternative therapeutic indications is also presented.

Abstract
This third article in the series on antidepressants reviews the monoamine-oxidase inhibitors (MAOIs). A chance discovery by chest clinicians led to the development of this class of antidepressant medications. Although MAOIs are not the first choice in modern-day drug therapy due to significant side-effects and drug interactions, they have played an important role in the development of the pharmaceutical management of depression. Focusing on moclobemide for clarity, this article discusses the pharmacokinetics and pharmacodynamics of this class of drugs, before discussing precautions and prescribing in special populations. A summary of MAOIs currently in use and their alternative therapeutic indications is also presented.

Mechanism of action
MAOIs prevent the conversion of monoamines into inactive products (Lehne, 2004). Monoamine-oxidase (MAO) is found in both neurons and non-neuronal cells within the body (Yamada and Yashuhara, 2004) and, depending on its presence, serves to inactivate different substances. In addition, two subtypes of MAO can be found in the body: MAO-A and MAO-B. Table 1 shows the sites and functions of each MAO subtype.

Therefore, by inhibiting MAO subtypes, neurotransmitter function is potentiated, thus relieving the symptoms of depression in the same way the SSRIs and TCAs do (Lovatt, 2010; Lovatt, 2011). However, as MAOIs are generally non-selective, they also inhibit the metabolism of dietary tyramine, leading to the accumulation of this compound in the body. Tyramine is similar in structure to amphetamine and has a sympathomimetic action on the body, which
causes the initiation of a ‘fight or flight’ response (Brent et al, 2005). This response, being superfluous in the depressed patient on daily medication under normal circumstances, results in the symptoms of ‘the cheese effect’: headache, hypertension, sweating, pallor, palpitations, neuromuscular excitation, and chest pain (Lehne, 2004; Brent et al, 2005). It is this concerning side-effect that has led to the MAOIs becoming second or third choice in the pharmacological management of depression. In an effort to overcome this limitation, a reversible, short-acting, selective MAO-A inhibitor, moclobemide, was developed and introduced on the market. Research suggests that the ‘cheese effect’ is less likely to occur with this drug, owing to its limited and reversible duration of action (Korn et al, 1986; Yamada and Yasuhara, 2004). It is worth noting that the selective MAO-B inhibitors, used as adjunctive treatments in managing Parkinson’s disease (Joint Formulary Committee, 2011) are also free from the potential tyramine interaction by the very nature of their mechanism of action.

ADME
Generally speaking, the pharmacokinetics of all first-generation MAOIs are similar, yet the literature on this topic is scarce (Yamada and Yasuhara, 2004; Brent et al, 2005). To enable focused discussion, this article will centre on moclobemide, the selective, reversible MAO-A inhibitor with an improved safety profile.

Metabolism
Following oral ingestion, moclobemide is absorbed quickly and extensively from the gastrointestinal tract (Brent et al, 2005; eMC, 2010a; 2010b). The presence of food is not known to reduce the extent of absorption but affects the rate at which the drug is absorbed (Schatzberg and Nemeroff, 2009). Protein binding of moclobemide is low, at approximately 50% (eMC, 2010a; 2010b), exerting a profound effect on the bioavailability of the drug following first-pass metabolism. This offers an explanation for the dosing schedule advised as ‘in divided doses’ (eMC, 2010a; 2010b; Joint Formulary Committee, 2011). Interestingly, the reduced bioavailability is noted to be less pronounced after multiple doses, at around 80%, whereas after a single dose it is as low as 60%, also providing further support of divided dosing in maintaining therapeutic effect. Moclobemide is extensively metabolized by hepatic oxidation, and part of this process is undertaken by the microsomal enzyme system cytochrome P450 (CYP450)—the isoenzymes responsible are CYP2C19 and CYP2D6 (eMC, 2010b). The metabolites produced are pharmacologically inactive (Schatzberg and Nemeroff, 2009). It is important to note that genetics can predispose patients to be ‘poor metabolizers’, due to a reduction or absence of CYP2C19 and CYP2D6 function. However, research suggests that the presence of alternative metabolic pathways enables adequate metabolism of the drug, and dose modification is not necessary (eMC, 2010b).

Excretion
Metabolites are excreted rapidly in the urine, along with less than 1% of the unchanged drug (eMC, 2010a; 2010b). Negligible amounts are found in breast milk (eMC, 2010b). The elimination half-life of moclobemide ranges from 2 to 4 hours in most individuals, which has a positive impact on patients requiring a change in antidepressant therapy. Whereas changing from an SSRI or a TCA requires between 1 and 5 weeks depending pharmacokinetic activity, those changing from moclobemide can continue straight onto the new therapy as the short elimination half-life—and therefore multiple dosing schedule—enables a smooth transition (Schatzberg and Nemeroff, 2009; Joint Formulary Committee, 2011).

Renal impairment
Despite its pharmacokinetic activity, prescribing

<table>
<thead>
<tr>
<th>Monoamine oxidase (MAO) subtype</th>
<th>Site</th>
<th>Inactivates</th>
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<tbody>
<tr>
<td>MAO-A</td>
<td>Brain</td>
<td>Noradrenaline Serotonin</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>Dietary tyramine (and other compounds)</td>
</tr>
<tr>
<td></td>
<td>Intestine wall</td>
<td></td>
</tr>
<tr>
<td>MAO-B</td>
<td>Brain</td>
<td>Dopamine</td>
</tr>
</tbody>
</table>

From: Lehne (2004); Brent et al (2005)
moclobemide for special populations appears somewhat surprising. Considering that the drug is rapidly eliminated renally, no precaution or dose reduction is required in renal disease, as this does not alter the elimination characteristics of the drug (eMC, 2010a; 2010b). Indeed, there is no ‘renal impairment’ heading under moclobemide in the British National Formulary (Joint Formulary Committee, 2011).

Liver impairment
Similarly, although the drug is extensively metabolized by the liver, precaution only need be taken in severe liver disease, with half or one third of the daily dose being prescribed (eMC, 2010a; 2010b). This dosing schedule is also suggested in those patients taking concurrent enzyme inhibitors, i.e. anticonvulsants, H₂-receptor antagonists, proton pump inhibitors, antiarrhythmics or antipsychotics.

Elderly patients
No alteration in dose is required with elderly patients, but co-morbidity and polypharmacy need to be considered to prevent potential drug interactions.

Co-medications
Although moclobemide cannot be taken with enzyme inhibitors, due to their role in the metabolism of the drug, moclobemide itself inhibits the isoenzymes CYP2C19 and CYP2D6, which is important to remember when reviewing a patient’s medication status.

In addition, patients who are being prescribed moclobemide must be advised to avoid sympathomimetics, which are present in many over-the-counter cough and cold remedies (Joint Formulary Committee, 2011).

Although the ‘cheese effect’ is said to be minimal with moclobemide, compared with irreversible MAOIs, the potential for hypertensive crisis is still very real when the drug is used in combination with sympathomimetics, as these medications usually promote the release of noradrenaline from sympathetic neurons, causing vasoconstriction and cardiac stimulation.

When used in combination with moclobemide this action is potentiated, as it inhibits MAO, which would normally inactivate noradrenaline, thereby reducing hypertension (Lehne, 2004; Kolecki, 2009).

Paediatric patients
Moclobemide and other MAOIs are not used in the management of childhood depression. The efficacy and safety of these medications are yet to be established in the paediatric population, and therefore they are not clinically indicated in the management of this patient group (BNFFC, 2010–2011; eMC, 2010a; 2010b).

Pregnancy and breastfeeding
There is a lack of clinical data establishing the safety of moclobemide in human pregnancy, although animal studies indicate no fetal damage. The manufacturers advise use only if the benefits outweigh the possible risks to the fetus (eMC 2010a; 2010b; Joint Formulary Committee, 2011).

It has been established that negligible amounts of the drug (around 1/30th of the dose taken by the mother) are eliminated via breast milk (eMC, 2010a; 2010b). However, it is advised that moclobemide only be given if the benefits of continued therapy outweigh the potential risks to the baby (eMC, 2010a; 2010b). Although the BNF states that the amount is too small to be harmful, it mentions the manufacturers’ advice to avoid use (Joint Formulary Committee, 2011).

Of all the antidepressant classifications discussed in this series, the MAOIs are the most restricted in their clinical indications. This could be justified by the seemingly limited function of MAO, and consequent relatively focused mechanism of action of MAOIs (Table 2).

Conclusion
In this third instalment, the development of the MAOIs has been discussed, along with the pharmacodynamic and pharmacokinetic properties that will impact on prescribing decisions. This article is not intended to be exhaustive; therefore, in the interest of maintaining patient safety and professional accountability, it is important to consult both the BNF and the different summaries of product characteristics before commencing any drug therapy regimen. Although the significant side-effects associated with the use of MAOIs may have had an impact on the use of this class of antidepressants, their development and use in clinical practice played a pivotal role in the development of the pharmacological management of depression and changed how clinicians envision mental health disorders.

Blackwell B (1963) Hypertensive crisis due to monoamine-oxidase
Drug Profile

**Key Points**

- Monoamine-oxidase inhibitors (MAOIs) were discovered by chance in the 1950s by chest physicians, and developed from a drug initially used in the treatment of tuberculosis.
- MAOIs are associated with significant side-effects, notably ‘the cheese effect,’ and are therefore no longer the first choice in psychopharmacology.
- MAOIs are CYP2C19 and CYP2D6 inhibitors.
- MAOIs are not recommended for use in children.
- Only one specific MAO-A inhibitor, associated with less interactions, is available at present.
- MAO-B inhibitors are used as adjuncts in the treatment of Parkinson’s disease.

**Inhibitors. Lancet** 282(7313): 849–51


eMC (2010a) Moclobemide 150 mg tablets. Available at: www.medicines.org.uk/EMC/medicine/21719/SPC/Moclobemide+150mg+Tablets/#PHARMACOLOGICAL_PROPS (accessed 23 February 2011)

eMC (2010b) Manerix 300 mg. Available at: www.medicines.org.uk/EMC/medicine/22288/SPC/Manerix+300mg/#PHARMACOLOGICAL_PROPS (accessed 23 February 2011)


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