Advances Pertaining to the Pharmacology and Interactions of Irreversible Nonselective Monoamine Oxidase Inhibitors

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Abstract: Recent advances clarifying the pharmacology and interactions of irreversible nonselective monoamine oxidase inhibitors that have not been considered in depth lately are discussed. These new data elucidate aspects of enzyme inhibition and pharmacokinetic interactions involving amine oxidases, cytochrome P450 enzymes, aminotransferases (transamminases), and decarboxylases (carboxylases) and the effects of tyramine. Phenelzine and tranylcypromine remain widely available, and many publications have data relevant to this review. Their effect on CYP 450 enzymes is less than many newer drugs. Tranylcypromine only inhibits CYP 450 2A6 (selectively and potently). Phenelzine has no reported interactions, but, like isoniazid, weakly and irreversibly inhibits CYP 450 2C19 and 3A4 in vitro. It might possibly be implicated in interactions (as isoniazid is). Phenelzine has some clinically relevant inhibitory effects on amine oxidases, aminotransferases, and decarboxylases, and it lowers pyridoxal phosphate levels. It commonly causes pyridoxal deficiency, weight gain, sedation, and sexual dysfunction, but only rarely causes hepatic damage and failure, or neurotoxicity. The adverse effects and difficulties with monoamine oxidase inhibitors are less than previously believed or estimated, including a lower risk of hypertension, because the tyramine content in foods is now lower. Potent norepinepherine reuptake inhibitors have a strong protective effect against tyramine-induced hypertension. The newly discovered trace amine-associated receptors probably mediate the pressor response. The therapeutic potential of tranylcypromine and L-dopa in depression and Parkinson disease is worthy of reassessment. Monoamine oxidase inhibitors are not used to an extent proportionate with their benefits; medical texts and doctors’ knowledge require a major update to reflect the evidence of recent advances.

Key Words: MAOI, phenelzine, tranylcypromine, pharmacology, interactions, adverse effects, toxicity

Abbreviations: AO - amine oxidase, BA - Biogenic amine, CYP 450 - cytochrome P450, DA - dopamine, DBP - diastolic blood pressure, EC - Enzyme Commission, FDA - Food and Drug Administration, INH - isoniazid, MAOIs - monoamine oxidase inhibitors, NRI - norepinepherine reuptake inhibitor, NE - norepinepherine, PLP - pyridoxal phosphate, SRI - serotonin reuptake inhibitor, ST - serotonin toxicity, SBP - systolic blood pressure, TA - trace amine, TAAR - trace amine-associated receptor, TCAs - tricyclic antidepressants

This review is selective in that it concentrates on the integration of new, and reinterpretation of old, knowledge about the 2 main irreversible nonselective monoamine oxidase inhibitors (MAOIs), tranylcypromine (TCP) and phenelzine (PLZ). Iso-carbazazid is less widely available, and there are no significant new data to review. The advances covered include the clarification of the extensive differences between TCP and PLZ, the

revision of the amine oxidase (AO) enzyme classification, the latest on interactions with cytochrome P450 (CYP 450) enzymes, tyramine metabolism, and the interesting new discovery of trace amine–associated receptors (TAARs). To appreciate these advances, some updating of knowledge about human AOs and the effects of tyramine on TAARs is required. The issue of the pharmacodynamic interaction of MAOIs with drugs that have serotonin reuptake inhibitor (SRI) activity is covered in detail in other reviews,12 that interaction is the frequently serious toxidrome of serotonin toxicity (ST), or serotonin syndrome; ST is not provoked by most tricyclic antidepressants (TCAs) (see below).

This is not a review of studies into the effectiveness of MAOIs. They are recommended or endorsed in almost all recent guidelines about the treatment of depression.3,11 Many specialists never use MAOIs,5–11 despite opinion and evidence of their superior effectiveness for various groups of patients.12–18 There had been few reviews of their clinical pharmacology, therapeutic, and interactions for many years, until Stahl and Felker’s article.19

ENZYME INHIBITION AND PHARMACOKINETIC INTERACTIONS

The AO Family of Enzymes

Amines are designated by the number of substitutions of the hydrogen atoms of the amonia moieties (NH3); primary amines have one substitution (ie, NH2-R1); secondary and tertiary have 2 and 3, respectively. Different AOs are more, or less, specific for particular amines (comparable substrate affinity data are sparse, but see Elmore et al20). Apart from MAO, other AOs have attracted little attention until recently. They have been considered “boring [with a] nomenclature that is confusing and shifting”; Tipton et al,21 tongue-in-cheek, believe this “adds to the excitement of often not knowing which enzyme is being referred to as semicarbazide-sensitive AO”.

These enzymes had been classified previously according to their overlapping inhibitor and substrate specificities. The nomenclature committee of the International Union of Biochemistry and Molecular Biology has recently changed the Enzyme Commission (EC) numbers for many enzymes referred to in this article (see http://www.ebi.ac.uk/intenz/index.jsp; accessed January 2010) as a result of new gene sequencing knowledge. The literature is thus confused with old and new names; for example, semicarbazide-sensitive AO has now been replaced by primary AO. The “non–monoamine oxidase (MAO) AOs” probably metabolize only substances that are primarily MAO substrates when MAO itself is inhibited20,21.

There is evidence that the structurally related hydrazine drugs, such as isoniazid (INH), PLZ, and carbipoda, inhibit the breakdown of histamine (and other amines) via inhibition of AOs, and that INH (and therefore possibly PLZ also) magnifies the effects of histamine intake in humans.22

Cytochrome P450 Enzymes

There are no clearly documented clinically relevant interactions in humans resulting from PLZ inhibition of CYP 450

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enzymes. However, it does weakly, but irreversibly, inhibit sev-
eral CYP 450 enzymes in vitro.31,32 Isoniazid is structurally
similar to PLZ and both are irreversible inhibitors in vitro.18
Isoniazid does have demonstrated clinically relevant interac-
tions in humans26–28 and in human liver microsomes in vitro.29
Phenelzine inhibits CYP2C19 and CYP3A4 isoforms in vitro,
lke INH, at the relatively weak Kᵢ of 30 μM.30 This would be
unlikely to cause inhibition if it were a competitive inhibitor, but
an irreversible inhibitor can produce an accumulating effect.
Uncertainties concerning the rate at which CYP 450 enzymes are
turned over mean it is difficult to predict whether such interac-
tions would ever become clinically significant. It is appropriate
to be aware of the possibility, because it does occur with INH.
Slow acetylators of hydrazines might be at increased risk for
adverse drug interactions and for hepatotoxicity with PLZ, as
they are with INH.30
Tranylcypromine has no irreversible inhibitor action but
does have CYP 450 competitive inhibitory activity, which is
not clinically significant at usual therapeutic doses except for
CYP2A6, where it is a potent and highly selective competitive
inhibitor (Kᵢ = 0.08 μM) with 60- to 5000-fold greater potency
relative to other CYP enzymes.31,32 The much lower affinity for
CYP2C19 (Kᵢ = 32 μM) is unlikely to be clinically relevant,
except perhaps at high doses, because blood levels are only
around 1 μM, and the same is so for other CYP 450 enzymes.33
A small number of drugs that are CYP2A6 substrates may be
affected at usual doses, particularly ifosfamide, cyclophospha-
dime, nicotine, tamoxifen, and propofol.34 However, CYP2A6
makes a minor contribution to their metabolism so the effect
would be expected to be minimal, except for nicotine. Tran-
ylcypromine raises plasma nicotine levels.35 People with low (vs
normal) CYP2A6 activity smoke fewer cigarettes per day.36
Cytochrome P2A6 inhibitors may be used as a new approach to
treat tobacco dependence,37 and those on TCP are likely to
smoke less.

Aminotransferases and Decarboxylases
The aminotransferases now have the name “transaminases”
and have the EC number 2.6.1.2, for example, alanine transaminase is
EC 2.6.1.2. Pyridoxal phosphate (PLP) is the active form of pyri-
doxine (vitamin B₆) and is an enzyme cofactor for many human
transaminases and decarboxylases (EC 4.1.1, now referred to as
in carboxy-lyases), about 50 different enzymes in all.23 Pyridoxal
phosphate forms hydrazone adducts with hydrazine MAOIs,
resulting in reduced enzyme activity. It is therefore possible
that PLP depletion will inhibit, to some as yet undetermined degree,
the many human transaminases and carboxy-lyases, for which it is
also a cofactor.30 Both alanine and γ-aminobutyric acid (GABA) tran-
saminase (EC 2.6.1.2) are inhibited by PLZ, resulting in a substantial
elevation in rat brain concentrations of alanine and GABA.37,38
Aralykline N-acetyltansferase (EC 2.3.1.87) catalyzes the for-
mation of N-acetylsertotonin, which is the rate-limiting step
in melatonin production. TCP is a substrate of aralkyline N-
acetyltansferase.39 Whether that has any relevance to its post-
prandial somnolent effects remains to be seen, but TCP does appear
to increase human plasma melatonin levels.40

Therefore PLZ, but not TCP, may have some as yet
imprecisely quantified effects on various transaminases and
carboxy-lyases.

Biogenic Amines and TAAs
The term biogenic amine (BA) is used to designate those
amines that act as hormones or local neuromodulators/trans-
mitters. Biogenic amines are produced from aromatic amino
acids by decarboxylation. These amines are categorized as
vasoactive (eg, tyramine and histamine) or psychoactive (eg,
phenylethylamine and tryptamine). Amines are metabolized via
oxidation by AOs, of which MAO is but one: other physiologi-
cally important amines, like histamine, are metabolized by di-
amine oxidase, which is inhibited by PLZ. Ingested BAs do not
usually reach nerve endings in significant amounts.

The term trace amines (TAs) refers to BAs present in
the central nervous system at very low concentrations (around
0.1–10 nM).41 Their function is a matter of debate, but they
likely play a role as neuromodulators of classic monoamine
neurotransmitters. Trace amines include 2-phenylethylamine,
tyramine, octopamine, and tryptamine. The specific receptors for
these TAs have been identified42–43 and called TAARs. They are
a novel class of G protein–coupled receptors, and they respond to
TAs but not to classic BAs. Trace amine–associated receptors are
expressed in the heart and play a direct role in mediating these
effects. Several TAs have direct inotropic effects on the heart,
mediated by TAAR1; these effects appear to be independent
from any sympathomimetic actions, which may occur at higher,
supraphysiological concentrations.44 One can expect rapid ex-
pansion of knowledge in this area.

From a food safety perspective, the most important pre-
cursors of BAs are histidine, which is converted to histamine;
tyrosine and phenylalanine to tyramine; arginine and ornithine to
putrescine; lysine to cadaverine; and tryptophan to tryptamine.
Ingestion of excessive histamine causes scombroidosis, or fish
poisoning, so-called because it seemed most common with the
scombroid family of fish (eg, tuna, mackerel), which have par-
ticularly high histidine levels. Cadaverine can cause, in rats,
hypotension, bradycardia, lockjaw, and paresis of the extremi-
ties. Spermine is toxic in rats at levels as low as 19 mg/kg of body
weight per day.46

Tyramine: Pharmacology and Effects
Tyramine has long been used as a pharmacological tool to
emulate endogenous norepinephrine (NE) release, and recent
data clarify its effects, especially in relation to TAA receptors.
Systemically infused, it produces NE spillover from the symp-
athetic neuroeffector junctions (mostly cardiac), a dose-dependent
increase of plasma NE, and increased systolic blood pressure
(SBP), but not diastolic blood pressure (DBP). Until recently,
tyramine was thought to produce a decreased DBP and also a plasma
dopamine (DA) increase. This was unexplained because it con-
trasted with infusion of NE, which increases DBP (eg, see Goldstein
and Holmes47 and Jacob et al48). That finding may now have been
accounted for by the discovery of a low-level impurity of DA in the
tyramine infuses,49 caused by oxidation of tyramine.

Tyramine increases SBP by increasing the force of cardiac
contraction (positive inotropic effect) and also by increasing
cardiac output by increasing the ejection fraction.47,50 This
appears to be via TAARs (see above) but, at greater concen-
trations, also by releasing NE. Other TAs (viz octopamine,
phenylethylamine, and tryptamine) produce a dose-dependent
negative inotropic effect. Because these other amines are usu-
ally coingested with tyramine in foods, this may partly explain
the lower pressor effect of tyramine in foods versus tyra-
mine capsules given as comparators, in addition to their lower
bioavailability.

It has always been considered contraindicated to give
MAOIs with l-dopa,51,52 because of a possible elevation of
blood pressure (BP). However, the most frequently quoted report of
this by Hunter et al52 concerned a single patient given 1 dose
of l-dopa (without a decarboxylase inhibitor), whose SBP rose
to 180 mm Hg. Teychenne et al\textsuperscript{53} showed that hypertension was minimal with i-dopa/carbidopa. Carbidopa is a hydrazine drug, which is an inhibitor of peripheral decarboxylase (EC 4.1.1.28—α-amino-α-amino-acid decarboxylase) that lowers the peripheral effect of DA, and it is also a MAOI.\textsuperscript{54} Thus, it appears that effective blockade of the peripheral effects of DA ameliorates or negates that pressor reaction. It may be useful to further explore the therapeutic potential of TCP and i-dopa in depression and Parkinson disease, because the risk of hypertension appears to have been overestimated.

**Tyramine Pressor Response (Cheese Effect)**

The BP elevation caused by tyramine in certain foods was not recognized until MAOIs had been in use for several years. Tranylcypromine was temporarily withdrawn in the United States (but not the United Kingdom) in 1964. The Food and Drug Administration (FDA) logged 500 cases of hypertension of which 38 had a cerebro-vascular accident, with 21 deaths.\textsuperscript{55}

Once the basic tyramine-restricted diets were implemented, the rates greatly decreased; when the FDA reviewed things in 1967, after dietary restrictions were introduced, there were 25 cases and 1 death.

It is hard to find reliably reported cases of fatalities after 1967. As an example, an apparent case\textsuperscript{56} actually involved a DA reuptake inhibitor (nomifensine). There is at least 1 more recent report of nonfatal cerebral hemorrhage.\textsuperscript{57}

**What Are the Signs and Symptoms of a Reaction?**

A reaction consists of a thumping heartbeat and a progressive increase in BP. The pulse may be decreased.\textsuperscript{58,59} If the SBP goes greater than 180 mm Hg, quite rapid onset of severe headache may occur, but headache is not a good indicator of hypertension. Tightness in the chest and pallor often occur. The increase in BP is proportional to the amount of tyramine ingested. Symptoms usually start 30 minutes to 1 hour after ingestion.\textsuperscript{60} Symptoms or headache starting more than 2 hours after eating is less likely to be due to BP elevation.

**What Is a Significant Degree of Hypertension?**

It is difficult to determine the degree of increase of risk-of-harm engendered by acute short-duration BP elevation for healthy individuals. Various common activities raise the SBP in excess of 300 mm Hg, for example, modest levels of exercise with weights.\textsuperscript{61} Also, rapid reduction of hypertension (ie, within 1–2 hours) may result in adverse effects.\textsuperscript{62,63} Treatment should be initiated only when there is definite evidence of acute and rapidly evolving end organ damage associated with hypertension (usually SBP >180 and/or DBP >120 mm Hg). Such treatment should not be initiated by psychiatrists because it requires admission to a critical care setting. Several recent reviews make strong statements about avoiding overtreatment of acute hypertension; for example, Flanigan and Vitberg\textsuperscript{62} state, “Often the urgency is more in the mind of the treating physician than in the body of the patient. . . . The compulsive need to treat treats the pathological in some physicians, especially during the early years in their careers.” It is noteworthy that pain and anxiety both exacerbate hypertension, so doctors should remain calm and use a benzodiazepine, while instituting measures to assess any possible developing end-organ damage. The most appropriate hypotensive agent will depend on the particular system affected (brain, heart, lungs, kidneys). Sublingual nifedipine is widely considered to be contraindicated because it has an unpredictable effect: it should rarely, or never, be given to patients to self-administer. These difficulties and considerations exemplify why psychiatrists are well advised to refer such cases rather than to attempt management themselves.

**Tyramine: Doses and Blood Pressure Response**

Tyramine causes a pressor (increased BP) response in normal unmedicated people. The oral dose needed to increase SBP by 30 mm Hg is referred to as the TYR30 and is approximately 500 mg (range, 200–800 mg).\textsuperscript{64} In fasted and unmedicated subjects given tyramine capsules (as opposed to a tyramine-containing meal). For tyramine mixed in a normal meal, the comparison is 1450 mg (range, 800–2000 mg).\textsuperscript{65}

Most tests have been done with fasting subjects, which causes tyramine to be absorbed more rapidly than it would be in a normal meal, which lessens the effect by about half; VanDenBerg et al\textsuperscript{66} found the maximum plasma concentration of tyramine was reduced by 72% when the dose was administered during a meal. Tyramine in a normal meal gave a TYR30 of 35 mg (range, 20–50 mg), 2.8 times higher than fasting, during TCP treatment.\textsuperscript{67} Likewise, the same dose of tyramine, in the form of a piece of cheddar cheese versus tyramine capsules, produced a rise in SBP of 11 mm Hg versus 45 mm Hg.\textsuperscript{55} The duration of the SBP increase was 126 minutes.\textsuperscript{65} Tyramine in liquids taken on an empty stomach should be regarded as about 3 times as potent as tyramine in food.

Biack and Antonin\textsuperscript{68} conducted a large study using tyramine capsules in fasting subjects. The median effective doses (ED\textsubscript{50}s) of tyramine (needed to generate an increase of 30 mm Hg) were as follows: no medication (n = 55), ED\textsubscript{50} = 437 mg (range, 200–800 mg); selegiline dose 20 mg, ED\textsubscript{50} = 96 mg; moclobemide dose 450 mg, ED\textsubscript{50} = 63 mg; PLZ dose 60 mg, ED\textsubscript{50} = 33 mg; clorgyline dose 10 mg, ED\textsubscript{50} = 43 mg; and TCP dose 20 mg, ED\textsubscript{50} = 16 mg. In other studies using tyramine in a meal, Zimmer et al\textsuperscript{68} found TCP dose 20 mg TYR30 = 35 mg, and Berlin et al\textsuperscript{65} also found TCP dose 30 mg TYR30 = 35 mg.

In the study of Korn et al,\textsuperscript{59} with a 65-mg initial dose of tyramine, and subjects on TCP 20 mg daily for 1 week, the pressor responses to the 65 mg tyramine “cheese snack” were marked (n = only 3). The SBPs rose by 70, 75, and 100 mm Hg, respectively. In the third case, phentolamine was infused for 2 hours to keep the SBP at 160 mm Hg.\textsuperscript{59} Blood pressure elevations reduced over 1 to 2 hours. An early article reported hospital inpatients who ate liver while on TCP (20–30 mg) that was subsequently estimated to contain tyramine 100 mg/kg.\textsuperscript{69} Symptom onset was within 1 hour. Headache was reported only in subjects with an SBP greater than 180 mm Hg (3 cases). Six of the 17 subjects had an SBP elevation greater than 150 mm Hg (maximum, 220 mm Hg). No morbidity was reported.

This information indicates that a significant proportion of patients on TCP would be expected to be able to ingest about 100 mg of tyramine, as part of a meal, and probably not get dangerous hypertension.

**The Protective Effect of NE Reuptake Inhibitors**

Combining MAOIs with TCAs is not difficult or dangerous, as is often presumed; it makes them safer: this was suggested by Pare et al\textsuperscript{60} 25 years ago. Note the exceptions are clomipramine and imipramine, which do have sufficient SRI potency to precipitate ST (see Gillman\textsuperscript{1,2} for a detailed analysis of TCA/MAOI safety and interactions). Norepinephrine reuptake inhibitors (NRIs) block the ingestion of tyramine into the presynaptic terminal, thus attenuating the pressor response, as many studies with TCAs, serotonin and norepinephrine reuptake inhibitors, and reboxetine demonstrate.\textsuperscript{67,69,71–78} The magnitude of the effect is proportional to the NRI potency at the human cloned NE transporter, and for more potent NRIs, such as clomipramine and nortriptyline, this is a sufficient effect in normal use to significantly lessen the risk of tyramine-induced hypertension (see Gillman\textsuperscript{5}).
Summary of Tyramine Dose and Hypertension

The evidence indicates that the interindividual variability in response to tyramine is around 3-fold. The minimum (oral) TYR30 with MAOI treatment, on an empty stomach, may sometimes be as low as 10 mg of tyramine for a small proportion of people, but is usually higher, about 25 to 50 mg. When tyramine is part of a meal, that figure can be multiplied by about 3 (to allow for lower bioavailability), which gives a mean of between 75 and 150 mg and a range of 25 to greater than 200 mg for an increase of 30 mm Hg, which is not dangerous. A potentially dangerous short-duration rise of SBP would probably need to be in excess of 220 mm Hg. Therefore, the estimate is that a substantial proportion of subjects would need to ingest 100 mg or more of tyramine, in a meal, to be at serious risk. Lower food tyramine levels now make that most unlikely if normal healthy food portions are consumed. Even with serious acute hypertension, the chance of an intracranial bleed, if it is left untreated, is less than 5%: the figures for the FDA for pre–diet-era incidents were approximately 4% (21 of 500) of reported cases that were fatal. A view about tyramine doses recently represented is reflected in the review of McCabe-Sellers et al, who suggest (somewhat unclearly) a conservative position: “The presence of 6 mg in 1 or 2 usual servings is thought to be sufficient to cause a mild adverse event, whereas 10 to 25 mg will produce a severe adverse event in those using MAOI drugs.” However, the references quoted by McCabe-Sellers do not support the likelihood of a severe reaction at doses of 10 to 25 mg of tyramine (see above, especially Hedberg et al). Rather, evidence indicates that 10 to 25 mg sometimes might be symptomatically significant, but not severe (in the sense of precipitating morbidity).

If sensible patient education and up-to-date diet information are provided, the possibility of morbidity (especially intracranial bleed) must be considered to be very low. Sensible patient education means not making dogmatic pronouncements (which in the past have been ill informed and incorrect) about banning certain foods, because there are unnecessary for a substantial percentage of patients who then do learn that doctors are often wrong, and who then ignore advice. A recent analysis in 2010, with extensive documentation and references on the tyramine content of foods and beverages, dispels many myths and indicates that levels are now lower than in the past.

Differences Between TCP and Phenelzine

Recent data clarify the major differences that exist between TCP and PLZ, which are summarized in Table 1. Pyridoxal phosphate depletion is an integral part of the mechanism of action of all hydrazine drugs including INH and PLZ (but not TCP). Many patients on INH for tuberculosis become vitamin B6 (PLP)–deficient and require supplementation. There are a case series duplicating that finding for PLZ and some case reports. Thus, routine measurement of pretreatment PLP levels, followed by checks after 1 and 3 months’ treatment, would seem advisable. Isoniazid and PLZ share the properties of neuropathy, neurotoxicity, and hepatotoxicity. Phenelzine is probably less hepatotoxic than other hydrazines, but there are cases of liver damage/failure associated with it. The risk factors for INH neuropathy (due to PLP depletion) are alcohol, diabetes, renal failure, malnutrition, pregnancy, and lactation. It often manifests initially as a burning in the feet. Pyridoxal phosphate is preventative in low dosage and curative in high dosage. Isoniazid can precipitate PLP-responsive seizures, not only following overdose, but also rarely at therapeutic doses. Phenelzine may be a link with PLZ-induced seizures. Phenelzine

<table>
<thead>
<tr>
<th>TABLE 1. Tranylcypromine and Phenelzine: Key Differences</th>
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<tr>
<td>Phenelzine</td>
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<tr>
<td>Potent antianxiety effect (GABA)</td>
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<tr>
<td>Side effects: sedation, edema, substantial weight gain</td>
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<tr>
<td>Elevated liver function tests, and hepatocellular damage</td>
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<td>leading, very rarely, to liver failure</td>
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<tr>
<td>PLP deficiency, neuropathy, and very rarely, neurotoxicity</td>
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<tr>
<td>(seizures)</td>
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<tr>
<td>Inhibition of AOs, hence possible histamine sensitivity</td>
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<tr>
<td>Inhibition of transaminases and carboxy-lyases,</td>
</tr>
<tr>
<td>including GABA transaminase</td>
</tr>
<tr>
<td>Nonlinear pharmacokinetics (blocks and is metabolized by MAO)</td>
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<tr>
<td>Addiction not documented, withdrawal reported very rarely</td>
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Tranylcypromine

No weight gain (usually weight loss, or neutral)
Little adverse effect on sexual function (possible benefit from dopaminergic action)
No inhibition of other AOs, transaminases, or carboxy-lyases
Addiction/withdrawal is reported rarely, usually only with greater than usual doses

Hydrazines affect GABA and inhibit glutamic acid decarboxylase and GABA transaminase, and hydrazine itself increases brain GABA levels. Phenelzine also raises brain GABA levels, which is probably the mechanism for its effect on anxiety states. That, along with sedation, edema, and weight gain, is the most prominent clinical difference from TCP. Clinical experience indicates PLZ has more adverse effects on sexual function than does TCP (many patients find TCP very satisfactory in that regard); that is supported by meta-analysis of trial results. Phenelzine potentiates hypoglycemia due to a direct influence on gluconeogenesis related to its hydrazine structure and potently inhibits adipocyte lipid storage and differentiation. The potent ability of PLZ to sequester toxic aldehydes may contribute to neuroprotective actions. A PLZ metabolite produced by MAO has been proposed as the cause of GABA and alanine elevation and increased brain ornithine, but PLP deficiency may also be implicated.

Phenelzine has nonlinear pharmacokinetics because it both blocks and is metabolized by MAO. Tranylcypromine does not appear to inhibit AOs other than MAO, and has a low level of adverse effects comparable to both newer second- and third-generation drugs and has high patient acceptability. The key differences are summarized in Table 1.

The Relativity of Risks With MAOIs

Monoamine oxidase inhibitors seem often to be characterized as “dangerous”; therefore, a reminder of some evidence about the relativity of risk with other drugs, for example, the nonsteroidal anti-inflammatory drugs and the selective serotonin reuptake inhibitors (SSRIs), may be useful. Nonsteroidal anti-inflammatory drugs caused 1200 deaths every year in the United Kingdom alone from gastrointestinal bleeds. Many patients would have taken these drugs for relatively minor aches and pains. Also, gastrointestinal bleeding is more frequent in patients taking SSRIs, causing morbidity and even death. It is therefore possible that there are a greater number of deaths related to bleeding associated with SSRIs than from MAOIs. One has not heard concern about that during 2 decades of SSRI use: “What the eye does not see the heart does not grieve over.”
Fatal cerebral bleeds are also documented associated with the increase in BP during sexual intercourse,\textsuperscript{130} weight lifting,\textsuperscript{61} and the use of ephedrine-related compounds that are over-the-counter drugs.\textsuperscript{131} The toxicity of MAOIs in overdose is approximately the same as typical TCAs, such as amitriptyline, at around 50 deaths per million scripts.\textsuperscript{132} These observations remind us that the degree of attention paid to the risks from MAOIs, and newer drugs, is relative and is covertly subject to various vicissitudes and influences.

**Hypothesized Amphetamine-Like Effects and Addiction**

An article by Youdim et al\textsuperscript{133} initiated the concern about amphetamine metabolites of TCP. In the ensuing 30 years, one further article also reported amphetamine metabolites after TCP overdose.\textsuperscript{134} An extensive study in both rats and humans\textsuperscript{135} failed to detect evidence of either amphetamine or 1-amino-3-phenylpropane, which suggests that opening of the cyclopropyl ring (Fig. 1) of TCP does not occur. Keck et al\textsuperscript{136} also failed to find amphetamine metabolites in 13 patients. Selegiline, which does not have the cyclopropyl ring, is metabolized into amphetamine.\textsuperscript{137}

Further evidence against the formation of amphetamine metabolites is that overdoses of TCP do not exhibit hypertension. Professor Whyte has reviewed all MAOI overdoses in the Hunter Area Toxicology Service database\textsuperscript{138,139} at this author’s request, and there was no elevation of BP, or any apparent BP difference between PLZ and TCP (personal communication). A drug that acted as both a releaser and a MAOI (ie, like taking the releaser amphetamine and TCP together) would be expected to act as a hypertensive combination and provoke a tyramine-like pressor reaction.

In 50 years of use, a very small number of TCP “addiction” case reports have been published.\textsuperscript{140-142} There appears to have been none with PLZ, although withdrawal symptoms have been reported.\textsuperscript{143}

**DISCUSSION**

The 2 most widely used older MAOIs, TCP and PLZ, have notable structural (Fig. 1), pharmacological, and clinical differences that are important but are usually ignored. The 2 potentially fatal pharmacodynamic interactions, which are ST and the pressor response to tyramine, are now well understood and straightforward to avoid. Tranylcypromine appears to have no problematic pharmacokinetic interactions; its potent selective inhibition of CYP 450 2A6 probably has no clinically important consequences except on nicotine. Phenelzine has no reported CYP 450 interactions, but may have some potential via weak, but irreversible, inhibition of 2C19 and 3A4. Phenelzine depletes PLP. Phenelzine’s inhibition of GABA transaminase raises GABA levels and may be the mechanism of the different profile of special effectiveness for anxiety symptoms.\textsuperscript{107} Tranylcypromine has adverse effect differences, some of them are advantages, when compared with PLZ (Table 1). Further advances are likely to lead to a better understanding of the selectivity differences (for MAO vs other AOs) between PLZ and TCP and of the precise mechanism of the tyramine pressor reaction.

There is a widespread resurgence of the opinion that MAOIs are not used to an extent proportionate with their efficacy/adverse effect/risk ratios, when compared with available alternatives.\textsuperscript{7,18,123,144} There is a greater degree of risk aversion with MAOIs, when compared with risks tolerated, or even ignored, with more familiar drugs. The lesser teaching and clinical exposure in medical training, lower knowledge levels, and reduced practical experience on the part of doctors are major determinants of this outcome. That, in its turn, has been related to what Cowen\textsuperscript{145} has termed “the pernicious influence of drug company marketing strategies,” which creates the high profile for newer drugs and drowns out attention to those perceived as commercially less marketable (especially because pharmaceutical companies control much of the postgraduate educational funding for doctors). Shorter,\textsuperscript{146} the eminent medical historian, has detailed these influences in a recent book. Also, it is probable that the attitudes of psychiatrists to prescribing MAOIs have had an impact on the willingness of pharmaceutical companies to invest in marketing and developments.

An up-to-date understanding of pharmacokinetic and pharmacodynamic interactions should now allow confidence in the ability to accurately predict and avoid problems. Therefore, it is logical to reassess MAOI use. The wisdom of hindsight indicates that there has been some overestimation of the supposed advantages of many newer drugs. This has resulted from selective publication of positive results, and nontransparency of negative ones, and the failure to systematically assess long-term adverse drug reactions\textsuperscript{147} or interactions. The short-term and incomplete assessment of adverse effects has produced a distorted picture of the relative merits of newer drugs that is taking decades to balance (eg, the bleeding tendency from SSRIs, mentioned above).

Directing attention and research funding to older drugs so that new techniques (eg, receptor pharmacology studies) can be applied to them continues to be an important consideration. A more proactive policy to teaching and exposure to the usage of MAOIs could be considered by relevant professional organizations to ensure that these drugs are used according to the evidence and clinical experience and not inappropriately displaced by those with novelty value and high advertising expenditure.

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