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Review Paper

Monoamine oxidase inhibitors: A review concerning dietary tyramine and drug interactions

P. K. Gillman

PsychoTropical Research, Bucasia, Queensland, Australia

Abstract

This comprehensive monograph surveys original data on the subject of both dietary tyramine and drug interactions relevant to **Monoamine Oxidase Inhibitors (MAOIs)**, about which there is much outdated, incorrect and incomplete information in the medical literature and elsewhere. Many of the drug interactions previously supposed to be serious are either non-existent or non-serious.

Very few foods now contain problematically high tyramine levels, that is a result of great changes in international food production methods and hygiene regulations. Cheese is the only food that, in the past, has been associated with documented fatalities resulting from hypertension. Nowadays most cheeses are quite safe, and even 'matured' cheeses are usually safe in healthy-sized portions. The variability of 'pressor' sensitivity to tyramine between individuals, and the sometimes unpredictable amount of tyramine content in a few foods, means a little knowledge and care are still required.

The few interactions between MAOIs and other drugs are now well understood and are quite straightforward to avoid and deal with. They are detailed and discussed here (by a recognised expert). MAOIs have no clinically relevant *pharmaco-kinetic* interactions. The only significant *pharmaco-dynamic* interaction, other than the pressor response to tyramine ('cheese reaction'), is serotonin toxicity (ST)—aka serotonin syndrome. That is now well defined and is straightforward to avoid by not co-administering any drug with serotonin re-uptake inhibitor (SRI) potency. There are no *therapeutically* used drugs, other than drugs with SRI activity, that are capable of inducing serious ST with MAOIs. Anaesthesia is not difficult or contra-indicated if a patient is taking MAOIs.

MAOIs are safe and straightforward to use, quite contrary to current popular opinion. Previously held concerns about MAOIs are mostly 'mythical' and misleading: either they are of greatly over-rated importance, or incorrect, or no longer relevant.

Check web site for latest V of this monograph

http://www.psychotropical.com/anti-depressants/maois

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

Key words

Monoamine oxidase inhibitors, hypertension, drug interactions, serotonin toxicity, decarboxylating enzymes, biogenic amines, washout intervals, tricyclic anti-depressants (TCAs), clomipramine, imipramine, tranylcypromine, phenelzine and isocarboxazid, isoniazid, narcotic analgesics, triptans, histamine, putrescine, cadaverine, tyramine, tryptamine, 2-phenylethylamine, spermine, spermidine, methylamine, trimethylamine, scombroidosis, hypertensive urgency, hypertensive emergency, sub-lingual nifedipine, subarachnoid haemorrhage, end-organ damage, anaesthesia, indirect sympathomimetic activity, adrenaline, noradrenaline, dietary tyramine, cheese reaction, L-DOPA, dopamine, chocolate, wine, beer, chianti, aged cheeses, cured meats, pepperoni, salami, sauerkraut, kimchee, soy sauce, miso, fish sauce, yeast-extract spreads, health supplements, Marmite, broad bean pods, fava beans

Abbreviations and synonyms

adrenaline (adrenalin or epinephrine), noradrenaline (noradrenalin or norepinephrine), serotonin (5-HT), serotonin/noradrenaline re-uptake inhibitor (SRI, NRI) or serotonin/ noradrenaline transporter (5HTT or SERT/NAT or NET), monoamine oxidase inhibitors (MAOIs), serotonin toxicity (ST), Biogenic amines (BAs), tricyclic anti-depressants (TCAs), indirect sympatho-mimetic activity (ISA), 3,4-methylenedioxy-methamphetamine (MDMA, ecstasy), reversible inhibitors of monoamine oxidase A (RIMAs).

Introduction and background

> If a man is offered a fact which goes against his instincts, he will scrutinize it closely, and unless the evidence is overwhelming, he will refuse to believe it. If, on the other hand, he is offered something which affords a reason for acting in accordance with his instincts, he will accept it even on the slenderest evidence. The origin of myths is explained in this way.
> Bertrand Russell, Proposed Roads to Freedom

This monograph covers diet (both food and drink) and drug interactions for those on MAOIs. It is intended to update, inform, and assist both medical and non-medical readers.

It is lengthy, not because the subject is difficult or complicated, but because exposing the myths surrounding MAOIs involves more than just contradiction. The subject of MAOIs is richly cloaked in myth and unfortunately a mythical assertion often repeated is more firmly established in the minds of uncritical thinkers than a truth stated but once.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

Interactions between **monoamine oxidase inhibitors (MAOIs)** and other drugs are not a difficult problem, contrary to current popular wisdom. These interactions have been well understood for some time but the knowledge has been slow to percolate to clinical practice. I have published various scientific papers relevant to this topic and am an internationally recognised expert on **serotonin toxicity (ST)** aka 'serotonin syndrome', which is the most serious potentially fatal interaction (see especially (1-6)).

MAOI interactions are neither frequent nor difficult to deal with, contrary to the impression generated by many standard texts. Experience shows problems and risks with MAOIs are less common than with SSRIs like fluoxetine, which has multiple potentially problematic interactions and yet is still widely used (7). Side effects are frequently less with tranylcypromine than with SSRIs, which is reflected by patients' generally stated preferences concerning optimum treatments (8-10).

Standard texts cover many issues within tight space constraints. They contain abbreviated discussion and information that causes confusion because 'standard texts' contradict the contents of detailed specialist texts, such as this monograph.

There is now a lot of quality data on tyramine in foods, and also on how much tyramine is likely to constitute a potentially serious problem (11). Previous opinions and advice have been based on old and sometimes inaccurate data.

This monograph surveys more original data on tyramine than any paper previously published. There are more than 200 new references, mostly recent, that have never been cited in the medical literature.

Biogenic amines (BAs), including tyramine, are heat stable: they are unaffected by cooking. Furthermore, decarboxylating enzymes are also heat-tolerant and may survive some cooking, allowing continued accumulation of BAs if cooked food is then poorly refrigerated. Storage of foods below 5°C is a crucial factor, and some domestic fridges fail to maintain temperatures of below 5°C. Fridge temperatures must be checked with an accurate thermometer.

Some common myths

Science must begin with myths, then progress to the criticism of myths.
Karl Popper

All the following statements are wrong:

- The diet is difficult.
- People cannot have cheese or red wine.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

- MAOIs have many dangerous interactions with other drugs.
- One cannot give an anaesthetic.
- It is difficult to swap to and from other drugs.
- One cannot combine them with tricyclic anti-depressants (TCAs).
- They have a lot of side effects.
- MAOIs cause hypertension/should not be given to hypertensive patients.
- Tyramine reactions are dangerous and need urgent treatment.
- Patients should be given nifedipine sub-lingually.
- Adrenaline cannot be used.

Units of measurement and quantities

All concentrations are given as milligrams (mg) of tyramine per kilogram (kg) or litre (L). Most food labels are legally obliged to quote information as content per 100 grams (abbreviation 100 g). Other abbreviations like: G, gm, gms and grms, are used, but 'g' is generally considered the correct notation.

Those living in non-metric areas will find it helpful learn to work in metric units: it is confusing to use standard servings/standard drinks or oz./pints. Some scientific papers still use different units of measurement in the same sentence (a patient weighing 180 pounds took a dose of 150 mg of a drug). That is like being told that someone is one meter 32.9 inches tall. Such practices are ultimately dangerous to people's lives. Especially for those in the USA, see the US metric association information:

http://lamar.colostate.edu/~hillger/common.html

and see also

http://www.newscientist.com/article/mg20827840.200-uks-chief-measurer-units-unite-the-world.html

How much tyramine produces a risk of serious hypertension?

For a majority of those who already follow healthy eating amounts and patterns the low tyramine diet involves almost no changes at all.

Although a small percentage of people may get a significant, but not serious or 'risky', blood pressure increase with only 10 mg of tyramine, a substantial proportion of people need to have closer to 50 mg (in a meal) to get a **blood pressure (BP)** increase meeting the definition of a 'hypertensive urgency' (i.e. systolic blood pressure

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

[SBP] > 180 mm Hg). BP levels in 'hypertensive urgency' range from 180 – 220 mm/Hg and do not engender an acute risk of serious consequences (e.g. sub-arachnoid haemorrhage).

For a detailed analysis of the evidence relating to tyramine 'dose' and blood pressure see below, and Gillman (1). Nevertheless, it is prudent to keep in mind that human responses to drugs and drug interactions vary from one individual to another and that there will always be exceptions to generalisations about doses and responses: that is one reason it is wise to monitor sitting/standing BP before and during treatment. See this pdf for instructions about BP monitoring:

http://www.psychotropical.com/images/pdf-downloads/MAOI_treatment_BP_so.pdf

It is easy to work out how much tyramine is in 10 or 100 grams or milliliters of any of these foods. People should familiarize themselves with what 10 g and 100 g looks like, and what sensible food portion sizes are. Those who eat 1 kg beef steaks, or half a kilo of cheese etc. will need to adjust to avoid trouble (and to be healthy). Some people (those with a BMI of more than 26) may benefit by consulting a dietician for explanations and education about how to eat healthily.

BMI (body mass index) is weight in kg divided by height in meters squared. i.e. for an average man = 70 (kg)/1.7(m)^2; or 70/2.89 = 24.22 Also see website information like http://www.win.niddk.nih.gov/publications/PDFs/justenough.pdf

Healthy portion sizes of cheese are approximately what is safe tyramine-wise: i.e. 100 grams of cheese in a meal is an unhealthily large portion. A healthy portion is 25 grams. Few cheeses (even 'mature' cheeses) contain more than 25 mg of tyramine in 100 grams (25 mg in 100 g = 250 mg/kg). So a 25 g portion contains only 6 mg of tyramine and that will not cause a significant blood pressure increase even in tyramine-sensitive individuals. Matured cheeses contain between 2 and 3.5 g of salt per 100 g (12), or 20-35 g/kg. The recommended daily salt intake has now been reduced by *some* authorities to around 1-2 g daily: adequate intake 1 g, upper limit 2-3 g. So 30 g of a typical cheese provides 1 g of salt.

Even if excessive tyramine is ingested and BP increase occurs, serious consequences are very unlikely. With present-day lower tyramine foods, it is difficult, if not impossible, to ingest the massive quantities of tyramine that led to patient deaths in decades gone by.

If excess tyramine is ingested it will usually mean nothing more than monitoring blood pressure for a 1-4 hours. In many mild ingestions,

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

which is all one is likely to see nowadays, BP will peak at about one hour.

Hasty and alarmist treatment of high BP by inexperienced doctors produces a risk of doing catastrophic harm. Current expert opinion strongly advocates that hypertensive urgencies should be treated conservatively. The safest 'out-of-hospital' intervention is a sedative dose of a benzodiazepine (see below), 'Hypertensive urgencies and emergencies due to tyramine and the occurrence of subarachnoid haemorrhage', for details.

Monitoring blood pressure while on MAOIs

It is quite simple to monitor blood pressure with an electronic BP monitoring device (upper-arm cuff, not wrist/finger cuff). All those on MAOIs should be schooled to keep a blood pressure record from the beginning of treatment (including a one-week pre-treatment base-line record). The drop in blood pressure on standing is a good indication of whether MAOIs are having a sufficient effect. There is further explanation on Psychotropical.com explaining blood pressure monitoring and MAOIs.

http://www.psychotropical.com/images/pdf-downloads/MAOI_treatment_BP_so.pdf

There are good reasons for blood pressure monitoring:

In my experience it is not possible to make logical and timely decisions about dose adjustment unless the BP is properly monitored. BP drop on standing (two measurements are essential) is the best measure of the effectiveness of a given dose and essential to optimal speed of adjustment to the final effective dose, whilst avoiding problems of excessive faintness, or even falling, from postural hypotension.

Although most people will only react to larger amounts of tyramine there is wide variation in the population and a minority of the population will experience greater BP elevation with relatively smaller doses of tyramine. Therefore, monitoring the BP will soon reveal those who are in the tyramine-sensitive group and warn of the need for extra care about diet (or addition of a noradrenaline re-uptake inhibitor (NRI)- see below).

Part 1

Introduction to dietary guide

'Dis-moi ce que tu manges, je te dirai qui tu es'

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

(Tell me what you eat, and I will tell you what you are)
Anthelme Brillat-Savarin Physiologie du Goût 1825

The drugs discussed in this monograph belong to the group called **M**ono-**A**mine **O**xidase **I**nhibitors (**MAOI**s). The enzyme **M**ono-**A**mine **O**xidase (**MAO**) has two sub-types, A and B. This information is most relevant for irreversible MAO-AB inhibitors (the most common are **tranylcypromine, phenelzine and isocarboxazid**) and less important for various other types of MAOI.

Persons on these drugs may be advised to keep some means of identifying the fact that they are on MAOIs readily available. Similar steps as may be taken with insulin dependent diabetes and those suffering epilepsy are appropriate; this is in case of accidents or emergencies. This may be: medical alert bracelet, and/or information in handbag or purse or wallet.

All treating medical practitioners should be informed if a patient is taking MAOIs, but most of them will not know what to do and will therefore offer inappropriate advice taken from out-of-date sources. Generally, advice on MAOIs should come from specialist psycho-pharmacologists, general psychiatrists usually have insufficient knowledge to manage MAOIs. Almost all the information on the Internet is significantly inaccurate, and even the information on sites of educational institutes is mostly out-dated and misleading.

The information provided here is authoritative; I have published multiple recent papers in prestigious scientific journals on the pharmacology of MAOIs and **tricyclic antidepressants (TCAs)** and their interactions and I have a great deal of first-hand practical experience, see especially references: (1-3, 5, 6, 11, 13-16).

The mechanism of tyramine formation

Tyramine formation in foods requires the availability of the amino acid precursor tyrosine and the presence of micro-organisms with amino acid decarboxylase enzyme activity. If favourable conditions for their growth and decarboxylating activity exist then tyramine, and other **biogenic amines (BA**) like histamine, cadaverine and putrescine may accumulate in foods.

Tyrosine, but little or no tyramine, is present at up to 20 mg/kg in animal protein sources, but is generally lower in plants (see below for exceptions). That is why fresh properly cold-stored foods are always safe. Animal protein can accumulate tyramine if allowed to go 'off'. Meat, fish etc. must be stored at a fridge temperature of less than 5°C. Meats that have been minced are especially prone to bacterial contamination. Poorly handled mince that has been improperly

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

refrigerated could accumulate significant tyramine quite quickly. That is why meat and fish processing must now take place at below 4°C by regulation in most countries. Few people in western society would now accept green rotten smelly meat, but eating meat like that was common practice in times gone by, and still is in some places.

Histamine, putrescine, cadaverine, tyramine, tryptamine, 2-phenylethylamine, spermine and spermidine are the most important BAs in foods (17-21); that is why smell (putrescine – putrid) is a helpful guide for what to avoid.

Measurement of biogenic amines

Much progress and refinement of measurement techniques of tyramine and biogenic amines in food has been made (22). Older estimations of tyramine concentrations may sometimes have been less accurate, especially because the isolation of amines from complex food matrices is not simple. Usually a derivatisation procedure needs to be applied to enable analysis by methods such as liquid chromatography (LC), or gas chromatography (GC) with various detectors, including a mass spectrometer (17, 23-26). Techniques are continuing to become better, faster, and less costly, so data are continuing to accumulate rapidly (23). Google scholar finds over 1000 references for 'biogenic amines food wine' between 2014 and 2015).

Toxicity of biogenic amines

Some BAs are toxic above a certain fairly low concentration. The amine most commonly implicated in toxicity in humans is histamine, which is responsible for the type of poisoning that occurs when spoiled fish is eaten. That is often called scombroidosis (see below). Recent reviews of the toxicity of amines give up-to-date information (17, 18, 27, 28).

The symptoms of a hypertensive reaction

A reaction is a progressive increase of **blood pressure BP** over 30 - 60 minutes (faster for liquids taken on an empty stomach) and may manifests first as a forceful thumping heartbeat. The heart rate usually becomes slower (29-32), in response to the increase in BP. If **systolic blood pressure (SBP)** goes above around 180 mm Hg quite rapid onset of severe headache is usual (although headache is not a reliable indicator of high BP). Tightness in the chest, paleness (pallor) may occur.

The degree of increase in BP is proportional to the amount of tyramine ingested.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

BP elevation starts soon after ingestion, usually around 30 – 60 minutes, and symptoms may occur soon after. Any symptoms, including headache, starting more than two hours after eating are unlikely to be due to a hypertensive reaction as the duration of the reaction is usually not more than 1 – 2 hours.

An SBP of 180 mmHg or more, sustained over 3 measurements in 10 minutes or so, performed in a calm setting with an accurate sphygmomanometer is now referred to as a 'hypertensive urgency'. If 'end organ' dysfunction is present it is called a 'hypertensive emergency'. End organ dysfunction is uncommon unless **diastolic blood pressure (DBP)** is greater than 130 mmHg.

In hypertensive urgencies the treatment aim is to reduce BP slowly over 24 – 48 hrs. Since tyramine reactions are self-limiting over 2 – 4 hrs., even for moderately severe ones, it is clear they will very rarely require intervention.

Tyramine in foods and beverages

Myth: The diet is difficult. One cannot have cheese or red wine

General comments on diet and tyramine

'The pleasures of the table belong to all men and to all ages, and of all pleasures remain the last, to console us for the passing of the rest.'
Anthelme Brillat-Savarin

This monograph reviews tyramine concentrations as indicated by a large body of food science research. Tyramine concentrations for ordinary foods depend on storage time and storage conditions. Modern food hygiene and handling practices and regulations in civilised countries mean that excess tyramine levels are unheard of in 'fresh' foods. That leaves those foods that are deliberately produced using micro-organisms, that is the subject-matter of a major part of this monograph.

Minimising or avoiding the very few high tyramine foods and beverages that do exist is easy and necessary whilst taking MAOIs. Only a few foods can build up the degree of excess tyramine (hundreds of mg/kg) that can greatly elevate the BP. The result of any BP reaction is in proportion to the amount of tyramine that is consumed i.e. **BP elevation is a dose-related effect**: that is why it is permissible and safe to cautiously 'test' small quantities of some foods e.g. your favourite cheese.

This monograph does not deal individually with compound foods, e.g. pizza. Such foods can have various types of ingredients that may have widely different tyramine contents. The total tyramine content

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

of such foods will depend on the individual ingredients, but a little common sense and calculation, from the information herein, will yield an estimate of the tyramine content.

Special starter cultures that have no decarboxylating micro-organisms in them have been developed and are now used in almost all food production processes. They are used by most cheese-makers, partly because they minimise the formation of undesirable 'off' flavours. They also minimise the proliferation of undesirable contaminant organisms (cf. yoghurt, below) and thereby greatly lessen, or even prevent, tyramine formation. Worldwide, attention has focussed more on 'food hygiene' and the European Union have an extensive program of monitoring and research, e.g. see 'Controlling Biogenic Amines in Traditional Food Fermentations' (33), and under 'Salami' below.

http://cordis.europa.eu/result/rcn/86612_en.html

Tyramine only accumulates in significant quantities when tyrosine is converted to tyramine by decarboxylase enzymes possessed by some, but not all, micro-organisms (see e.g. (34)). The only foods that have enough tyramine in them to cause significant reactions are those that have been subjected to the action of these particular types of micro-organisms. However, modern food hygiene standards are such as to make that increasingly rare, because biogenic amines, including tyramine are monitored as part of food quality and hygiene audits (17, 35).

A potentially significant elevation BP can only occur if a relatively large amount of tyramine is eaten or drunk. For those on MAOIs most people (around 50% of the population) will need to ingest at least 25 mg of tyramine. A small proportion of people are more sensitive to tyramine and in such subjects 10 mg may be enough to cause a measurable or symptomatic BP elevation. Most foods with elevated tyramine (like matured cheeses) actually have no more than 250 mg/kg. Therefore, quantities of up to 100 grams of such a cheese (and that is a large portion size), may be consumed without consequence by most people. Further discussion is in Finberg & Gillman (11).

The earliest work on this subject remains instructive. Barry Blackwell described the cause-effect nature of the 'cheese reaction': The original papers by Blackwell (36-45), summarize very well most of the basic points that are in this monograph. For those who like to know more about history Blackwell has written about it recently on the web site of the recently founded 'International Network for the History of Neuropsychopharmacology (INHN)' here:

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

http://www.inhn.org/controversies/barry-blackwell-adumbration-a-history-lesson.html

'The wheel is come full circle, I am here'
Edmund, King Lear

Barry Blackwell has expressed his appreciation about this monograph and still feels that the chemist, Rowe, who made the key observation (his wife was taking 'Parnate'), has not had sufficient recognition. Although Barry described Rowe's role in the story in a subsequent paper, his name was not in the initial publication, and Barry still regrets that. It is therefore satisfying to be able to 'close the circle' by refreshing our memories of the subject's history in this review.

Seminal early research on the tyramine content of cheeses was done by Kosikowski, e.g. (46). It is interesting to note that the series of papers he authored in the 1950s have never been cited in the medical literature, except by Blackwell (41)*. So his efforts also have had insufficient recognition.

*derived from Google scholar 'cited by' links

Blackwell noted that almost all cases of the 'cheese reaction' then reported (1965) implicated cheddar cheese, some of which had been assayed as having around 3,500 mg/kg of tyramine (47), which greatly exceeds (by about two orders of magnitude) the values generally found in any assays of similar cheeses in the current era.

The explanation for the absence of data about tyramine in the medical literature is that medical writers have only searched for papers using the medical literature databases (i.e. 'PubMed' etc.). However, such databases do not include many of the food science related research journals, and it is in such journals that the data actually reside. A recent example of only citing papers from the medical literature databases is exemplified by the citations in Flockhart's 2012 review (48), which although calling itself an 'update', has no original references about tyramine after 1996, and no data at all from the food science literature. Not much of an update.

Most of the references herein come from the food science literature, so a majority of them will not be located by a 'PubMed' search.

Only very rarely encountered foods will now have high tyramine concentrations, such as 1,000 mg/kg, or greater.

Dairy products, cheeses etc.

Cheese: 'Milks' leap towards immortality'
Clifton Fadiman

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

Most cheeses now have low tyramine levels (< 10 mg/kg), whether they are hard, semi-hard, acid-curd or soft (24, 26, 49-52).

It is likely that the unusually high concentrations of 1,000 – 3,000 mg/kg or more reported occasionally in older samples will no longer occur because food regulations have driven widespread reductions of tyramine levels, especially through the use of starter cultures (17, 52).

Matured and 'artisanal' cheeses can sometimes develop high concentrations of tyramine (~ 1,000 mg/kg), although many are surprisingly low. 'Matured' usually means aged for more than 3 months (typically 6 months or more), rather than just a few weeks.

Contrary to what one might assume from the (lack of) data in the medical literature (48, 53-56) there have been thousands of tyramine estimations performed from cheeses all over the world: a selection of studies with extensive and varied sampling is given here to illustrate this.

Almost all commercial lower priced 'processed' and 'supermarket' cheeses are low in tyramine (always <200 mg/kg, usually in the range of 0 – 50 mg/kg) because 'supermarket' type outlets require large quantities of produce (i.e. industrial-scale, not artisan), and low prices do not pay for long warehouse ageing (i.e. more than 3 months).

Bunkova et al. recently reviewed the widely marketed Edam-style cheese (50). As they point out:

> "Optimum ripening time of these products is 6-10 weeks, usually at a temperature of 10-14 °C. However, nowadays, young cheeses (2-4 weeks old) are delivered to retail by many producers for economic reasons."
> They studied tyramine levels during maturation and storage and noted particularly that "In all ripening/storage regimes tested, the highest content of tyramine, putrescine and cadaverine was found in the edge [rind]. On the other hand, the lowest content was detected in the cheese core."

They found that tyramine levels increased in approximately linear fashion over time, being 60 mg/kg at 60 days and reaching a maximum of 120 mg/kg at 100 days in the outer layer (rind) and less in the core, 70 mg/kg.

Processed cheese

Processed cheese generally has low levels of tyramine. Ibrahim et al. analysed 45 samples of processed cheese made from a variety of types and found the mean was ~ 200 mg/kg for cheddar styles, and 100 mg/kg for Gouda styles, however, there were a small number of samples that were rather higher, the maximum being 800 mg/kg. (57). Note, these were shelf samples from Egyptian retail outlets,

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

who knows how long they had been on the shelf? Or at what temperature?

Classic matured (hard, semi-hard) cheeses

French

Francophiles may be surprised to be reminded that there are relatively few French hard cheeses and even fewer that are available outside France, examples are: Cantal, Comté, Emmental (generally produced industrially) and Mimolette (Edam-like).

Comté AOC: Mayer: tyramine 0 mg/kg (26). Comté is essentially the same as Swiss Gruyere, but still mostly in the hands of small producers, whereas Swiss Gruyere is almost entirely large-scale co-operatives. One would therefore predict the Swiss types would be even lower in tyramine.

Cantal: Mayer: 0 mg/kg (26).

Italian

Parmigiano Reggiano: aged 24 and 30 months, tyramine 20 – 150 mg/kg (51), but Mayer (26) found levels < 10 mg/kg in the 6 samples he tested*

*Table 2, note the blank spaces in this table denote 'undetectable' as confirmed with Mayer (personnel communication).

Grano Padana (12 & 22 months old) all samples tyramine < 130 mg/kg. Mayer (26) found undetectable levels.

The Spizzirri paper included a wide range of cheeses (mostly Italian), Grana Padano, Pecorino, Provolone, Ripened goat cheese, Emmentaler, Taleggio, Bel Paese and more, none of which had more than 200 mg/kg of tyramine.

Italian pecorino (58). This paper reviews tyramine levels in a wide variety of pecorino cheeses made from all the different significant producing regions of Italy. Some of them are very 'artisan' type cheeses and there is great variation. Many have quite low levels in the region of 100 - 200 mg/kg, but one particular example, Pecorino Del Parco Di Migliarino San Rossore, exceeds 1000 mg/kg.

British

Cheddar: young cheddar (4 weeks) all tyramine < 50 mg/kg, at 36 weeks maturation all samples < 160 mg/kg (59) and Mayer (26) found levels of tyramine 0 mg/kg.*

*Note the great difference from the old assays, one or two orders of magnitude, < 50 mg/kg vs. the old value of around 3,500 mg/kg of tyramine (47, 60).

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Dutch

Gouda is a very widely copied cheese style which when young is semi-soft and hardens with age. Real aged Dutch Gouda is called "Oude kaas (10-12 months old), Overjarige kaas (18 months old). Tyramine levels will vary with age, younger ones seem to have very low levels, older ones 100 – 250 mg/kg (26).

Dutch-type semi-hard cheeses mostly tyramine < 50 mg/kg, max 250 (61, 62).

Swiss

Gruyere: tyramine < 100 mg/kg (51)

Emmental: tyramine 0 - 68 mg/kg (26) and Spizzirri (51) 16 mg/kg.

Other cheeses (non-hard)

Brie and camembert styles (un-washed rind)

Normally these cheese styles (mould-ripened soft cheeses) are only matured for 4 weeks before release, so low tyramine levels are expected. Tyramine concentrations are less now than in the past because of starter cultures and better storage (see below for older results). Thus it is no surprise to find that the latest estimations using modern assay techniques give very low tyramine levels of < 10 mg/kg.

Mayer et al. looked at examples from Austria, Denmark and France and found negligible tyramine levels (maximum of 5 mg/kg) in 5 different types of un-washed rind soft cheeses (26).

Some older papers have reported much higher levels which may be explained by poor production and storage and/or faulty assays; Horwitz (63, 64) found tyramine ~ 100 mg/kg. Other older papers found undetectable levels (46).

Colonna (1970s): Camembert (French), 20 samples, most had low levels of tyramine ~ 100 mg/kg, but showing large variation up to1800 mg/kg (65).

De Vuyst: Brie tyramine 0 – 400 mg/kg, camembert very low, maximum 20 mg/kg (60).

Voight: Brie tyramine 0 – 260 mg/kg (66).

Washed-rind cheeses

Washed rind cheeses (Epoisses is the classic) seem to have even lower tyramine levels than unwashed rind like Brie and Camembert Styles, (67, 68).

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

Others

Acid-curd cheeses. Some are coagulated (curdled) using rennet, but some undergo curdling by bacterial lactic acid fermentation and these might be expected to contain a little tyramine. See below under 'Austrian' (49).

Feta style: generally low tyramine but 'older' examples creep up a bit to 250 mg/kg at 120 days of age (69).

Austrian

A recent (2013) and extensive analysis of 47 different Austrian cheeses, particularly ripened acid-curd cheeses, is detailed in Fiechter et al. (49). Most have low tyramine levels of < 100 mg/kg, only 18/47 samples were > 100 mg/kg). The median concentration for tyramine was 30 mg/kg. One sample of aged acid curd (Ennstaler Steirerkäse with crumble texture) was the highest was at nearly 2,000 mg/kg).

Roquefort and Roquefort styles

Roquefort and Roquefort style 'traditional' cheeses (all made with Penicillium roqueforti), these include: Fourme d'Ambert, Bleu de Bresse, Gorgonzola, Stilton, Cabrales, Gamonedo and the 'industrially-produced' types Danish Blue, Bleu d'Auvergne, Edelpilzkäse, Mycella.

Roquefort 4 samples: tyramine 0 mg/kg (26).

Blue cheese, Czech (70, 71): the mean and median being tyramine 380 mg/kg and 289 mg/kg, respectively) and, different cheeses (vats) varied widely, from 10 mg/kg, to 875 mg/kg.

Non-matured cheeses, yogurt, milk

Cheese spreads

These occupy an in-between position in that it depends on what they are made from: some higher quality cheese spreads are made from proper vintage cheeses, a few of which may be relatively high in tyramine. As an example, 'Parmareggio' cheese spread clocked in at tyramine 40 mg/kg, not high, but significant if one was to eat a whole tub of it (51). On the other hand, most spreads are like commercial cream cheeses and contain no tyramine.

Unripened cheese styles

Fresh non-matured, i.e. unripened/unaged, cheese styles, and yoghurt, are always safe because milk itself has no tyramine, e.g. curd

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styles, *fromage frais*, mascarpone, cream, ricotta, mozzarella, cottage cheeses, bocconcini.

Spizzirri et al. assayed multiple samples, tyramine: 0 mg/kg (51).

Unripened cheeses: 10 samples (72) tyramine < 0.5 mg/kg.

Goats cheese (73), unripened 'frais' styles, usually tyramine < 5 mg/kg, many 0 mg/kg (51).

Aged goats cheeses: usually low tyramine < 10 mg/kg (51), but some may be higher, e.g. 70 mg/kg (73).

Milk and yogurt

In France, the regulations are strict. To be called yoghurt milk must be fermented by *Lactobacillus bulgaricus* and *Streptococcus thermophilus* (no decarboxylase activity, so no tyramine), via starter cultures. Bacteria have to be at least at 10,000,000 CFU/g till the end of shelf-life. That means it is virtually impossible for tyramine producing bacteria to gain a footing: so yoghurt has no tyramine. Novella-Rodriguez, 5 samples, no tyramine (72, 74).

Cho, Korea, Yoghurt, 8 samples, max tyramine of 4 mg/kg (75).

But, be warned, if you are holidaying in the Himalayas, watch out for Tibetan traditional fermented yak milk which may have tyramine 900 mg/L (76).

Fermented vegetables/cereals (Inc. sauces)

Fermented cereals: Background history

A little caution is appropriate regarding sourdough bread because it can accumulate tyramine to a level of several hundred mg/kg, as can other similarly prepared foodstuffs widespread in other countries (see below).

Almost from the dawn of agricultural practice humans have learnt to increase the palatability and digestibility of legumes (see Soya) and cereals through the use of fermentation, both with yeasts and bacteria. Yeast fermentation does not give rise to tyramine, but bacterial fermentation can do, depending on the types of bacteria and their decarboxylating activity.

The United Nations food and agriculture organisation (FAO) classify cereal-related products a) on the basis of raw cereal ingredients:

a) wheat-based foods e.g. bouza, kishk
b) rice-based foods e.g. busa
c) maize-based foods e.g. ogi, bread, kenkey

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d) millet based foods e.g. kunuzaki
e) sorghum based foods e.g. pito, ogi, bogobe, kisra, burukutu, kisra, injera
f) barley based foods e.g. beer

and b) on the basis of texture:

a) liquid (gruel) e.g. ogi, mahewu, burukutu, pito, uji
b) solid (dough) and dumplings e.g. kenkey, agidi
c) dry (bread) e.g. kisra, injera

There are many dozens of local names for such preparations, for details consult culinary works, Wikipedia, google etc.

Sourdough bread

In the modern world the most prominent cereal-related solid-food vestige of these ancient fermentation practices is sourdough bread. This differs from normal bread because it utilises bacterial activity in the starter culture for making the dough. Just as with all other fermentation techniques this will not produce significant levels of tyramine if the usual modern standardised starter cultures (with minimal decarboxylase activity) are used, as is now generally the case with commercial production. However, Artisan producers may well utilise cultures with greater decarboxylase activity. Therefore, their products may sometimes contain significant levels of tyramine.

Recent research indicates what would be expected by anybody who has understood the contents of this monograph. Preparations made with standardised starter cultures are generally low in tyramine but there are some exceptions, usually home-made and locally made Artisan-type produce. Rizzello found tyramine levels of around 700 mg/kg in sourdough fermented wheat germ (77).

Özdestan has investigated various similar Turkish foods and found lowish tyramine levels (78, 79): like kumru (ten samples of from different manufacturers in Turkey) < 5mg/kg, shalgam (20 samples) < 50 mg/kg, and tarhana (20 samples) 50 – 100 mg/kg.

Marmite, Bovril, Promite, Vegemite etc.

It is likely that changes in the way these products are prepared in recent years have lowered the tyramine content; but there are not many measurements to rely on.

Marmite is made from the residual brewer's yeast and the first production facility was near the Bass beer brewery in Burton on Trent: production started in 1902. It had/has relatively high amounts of biogenic amines ~ 320 mg/kg of tyramine (80) and 650 mg/kg of tyramine (81). Both those are rather less than Blackwell's original

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estimate (42, 43, 45) of around 1,500 mg/kg, which may represent a change in production technique, or inaccuracies in measurement. One would need to take 30 ml to get 10 mg tyramine, which is more than is usually consumed.

Marmite-like spreads are somewhat similar to soy sauce and 'miso' which also involve 'fermentation' of brews containing non-animal proteins. They are usually used in small amounts, which can be safely eaten. A teaspoon (5 ml) of 'Marmite" would have only 5/1000 x 300 mg of tyramine, i.e. only a couple of milligrams.

Soy bean products

All *fermented* soy bean products like sauce and paste are prone to have significant tyramine levels.

For a list of fermented soy bean products see Wikipedia https://en.wikipedia.org/wiki/List_of_fermented_soy_products

Non-fermented products like (most) tofu have no tyramine (82).

Soy sauce, natto, miso and sufu etc.

Soy sauce is made from steamed soybeans, roast wheat and Koji fungus, the moromi mash may then ferment for as much as 2 years after which it is filtered and pasteurised. Soya beans have no tyramine; it is produced slowly during the fermentation reaching typical concentrations of ~150 mg per kg (litre) after many months. Miso is similar. The story with these products is an echo of the fermented cereal picture, just with beans as opposed to grains, so levels may vary (83-85).

Japanese soy sauce: Maximum tyramine 940 mg/L (i.e. approx. 1 mg/ml). Most samples measured have ranged between 10-200 mg/L (86). Maximum tyramine concentrations in the past may have been as high as 1000 mg/L, so 25 ml of that would have contained 25 mg of tyramine.

Most supermarket Soy sauces actually have tyramine levels around 100 mg/L.

Yongmeia (87), 40 samples of Chinese soy, mostly tyramine less than 200 mg/L (20 of the 40 were < 100 mg/kg). The total content for the five biogenic amines in these samples was 497 mg/L with a range from 41.7 to 1357 mg/L. The concentrations for each of the five amines were: tyramine 0–673 mg/L, histamine 0–592 mg/L, cadaverine 0–550 mg/L, spermidine 0–486 mg/L and spermine' 0–145 mg/L.

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Stute (88), 23 samples soy, all low tyramine < 200, except one clocked a staggering 6,000 mg/kg (dead rat in the vat? or just a typo for 600?).

Miso, 5 samples tyramine ~ 20 mg/L (75), and Kung 40 samples: all < 50 mg/L (89).

Other soy derived products like miso soup and sufu (75, 90) generally have similar concentrations. Miso, 5 samples tyramine < 25 mg/kg (75), and soy sauce tyramine < 50 mg/kg (75). Sufu from Taiwan (91), and Miso 40 samples tyramine all < 10 mg/kg (89) but some rather higher (92).

'Natto' is another fermented soya bean preparation that sometimes achieves high tyramine levels, although < 100 mg/kg is typical (85, 93).

Soybean pastes ('Doenjang' etc.), of 23 samples most had undetectable levels, but a couple were > 1,000 mg/kg (94).

Fermented sauces: Animal

Fish sauces

In classical Roman cooking fish sauce was called garum or liquamen. They are ubiquitous now, but have long been deeply rooted in Far Eastern cuisine. Seafood, often anchovy, is allowed to ferment ~ 140 - 200 days. Names: Nuoc-Mam (Vietnam), Nam-Pla (Thailand), Budu (Malaysia), or Patis (Philippines) ketjap-ikan (Indonesia), ngapi (Burma), ishiru or shottsuru (Japan), colombo-cure (India Pakistan), yeesu (China), aekjeot (Korea). For more see Wikipedia, and for recent reviews refs (19, 75, 88). NB Cho is in Korean, but the tables of values are readable.

They will, like everything, vary a bit with producer and hygiene quality, but seem usually to be OK, 200 – 500 mg/kg (bearing in mind it is, like soy sauce, a condiment, so if used in modest amounts (no more than ~ 20 grams) will be safe (95).

Korean fermented fish products tyramine < 50 mg/kg (75), liquid fish sauce made from a variety of things, scallop, squid etc. tyramine average 350, max (anchovy) 600 mg/kg (75).

Stute (88), 45 commercial fish sauces from the Far East, most < 200 mg/kg, maximum 588 mg/kg for tyramine.

Worcestershire sauce is fermented and contains anchovies (at least the original 'Lea & Perrins' version). There are many different producers of such sauces called 'Worcestershire' or 'Worcester' and there is no data on their tyramine content, but it is reasonable to

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assume it will be variable and similar to other fish sauces, probably lower. If used in condiment quantities it is unlikely to add a significant tyramine load to a meal.

Meat and fish products

Fresh and frozen meat and meat products are safe, but if they are not fresh, i.e. if they have been subject to decomposition by micro-organisms, then they could be risky. Fresh liver has no tyramine (96), but if stored badly or past its 'use by' date when purchased, and then kept in a domestic fridge that is not cold enough, may become risky (97, 98). The Hedberg paper (97) is a great illustration of good observation and investigation.

Ordinary commercial beef is not usually aged and concentrations of tyramine are likely to be < 10 mg/kg. Galgano, 7 mg/kg after 8 days at +4°C (99).

Similarly, liver patés (and similar meat or fish pastes) are safe if freshly made and properly refrigerated (i.e. *below* 4°C), especially because such foods are normally consumed in small portions. No specific modern data is available as yet, but the lessons enumerated herein tell us what is likely. Liver (100) has no tyramine, but once processed and contaminated with bugs it is an ideal culture medium, so any laxity in hygienic preparation, storage time and temperature will result in a steady increase in tyramine. Concentrations of tyramine 100 – 500 mg/kg are likely in contaminated and badly stored product after a week or two.

Meat, fresh

General

Fresh meats contain no significant amounts of tyramine, for a review of amines in meat (and vegetables) see especially Kalac (101-103). Also, for discussion see (104-106).

Stored *chilled* meats are safe (i.e. < 10 mg/kg) (99, 102, 107). Beef: stored at –18°C for 178 days, tyramine max tyramine <4 mg/kg (107, 108).

Poultry

Chicken: refrigerated for 20 days at a temperature of +4$^{\pm}$1°C in a domestic refrigerator. Tyramine level at one day - 3 mg/kg, 20 days - 15 mg/kg (109-112). Moreira found well stored product < 5 mg/kg.

Poultry: insignificant levels (113-117).

Duck: tyramine 0 (116).

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Minced and ground beef

Minced and ground beef and 'hamburgers' are potentially problematic because any contaminant bacteria are mixed into a medium (mince) with a large surface area, which may then be sub-optimally stored. It is therefore reassuring to find assays have found negligible levels of tyramine < 3 mg/kg (118). It might also be observed that, in North America alone, they consume millions of burgers per year and there are no reports of tyramine reactions associated with burgers.

Beef

Beef (stored above 0°C) can have significant tyramine concentrations: stored at +4°C for 21 days, 60 mg/kg, and after 36 days at +4°C 120 mg/kg (105). Such meat is usually only available in the restaurant trade (at a high price!), but could contribute to excessive tyramine intake as part of a gourmet meal. However, there are no reports of reactions with beef in 50 years (cf. liver, a couple of reports of reactions in 50 years).

Pork

Pork and fresh pork products, not surprisingly, have no tyramine (114-116).

Offal

Fresh offal contains no tyramine. Kidneys, liver, duck giblets etc (100, 114, 116, 119, 120), all had no tyramine.

Sausages, pâté, meat pastes

These have minimal tyramine unless poorly prepared or stored (121-123).

Meats, preserved

Dry-cured meats

As with all *dry cured* meat products (as opposed to fermented ones) only low concentrations of tyramine are expected, Lorenzo found < 5 mg/kg (124), which agrees with (125). So 'Parma ham', pastirma, jamon, prosciutto, coppa etc will all be safe.

Fermented sausages

Concentrations of tyramine depend, as would be predicted, on the hygienic quality of the meat used and the strains of bacteria involved. Those produced with frozen meat (low temperature processing)

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usually have maximum concentrations of about 100 mg/kg. The improved starter cultures, now widely used, show a lack of, or much diminished, amino acid decarboxylase activity which results in lower concentrations of BAs (34, 126-130).

In their 2003 paper, 'Biogenic amines in dry fermented sausages: a review' Suzzi reviewed 20 studies from all over Europe (131) and found tyramine was usually below 200 mg/kg, very few samples were higher (125). Suzzi '*In the several reports concerning the Spanish dry fermented sausages Chorizo, Fuet, Sobrasada and Salsichon, tyramine was generally detected at the higher concentration (exceeding 600 mg/kg in some sausages with mean values of about 200 mg/kg)*.'

In Spanish fermented sausages Chorizo, Fuet, Sobrasada and Salsichon tyramine was detected at up to 600 mg/kg in some sausages, with mean values of about 200 mg/kg (132).

French sausages, both artisanal and industrial, had tyramine maxima of 270 mg/kg (131, 133).

Papavergou (134): 50 samples of dry fermented sausages sold in Greece, mean 100, max 500 mg/kg.

Hygiene and low temperature processing continue to improve steadily, more recent surveys find generally lower concentrations (128, 135, 136).

Latorre-Moratalla et al. is a good recent review: they found an average of 150 mg/kg, max < 200 mg/kg. The study received financial support from the European community project: 'Assessment and improvement of safety of traditional dry sausages from producers to consumers' (QLK1 CT-2002-02240, Website: www.clermont.inra.fr/tradisausage/). It is a good example of the efforts being made to monitor and improve hygiene standards.

Preparations of stock cubes, powders, bouillon, etc.

These are not prepared by fermentation but are flavoured extracts and reductions, therefore they are most unlikely to be high in tyramine. Populin tested broths (homemade or canned products from the market), soups (ready-to-eat soups, condensed soups and creams), soup bases (bouillon cubes, pastes and granulated powders), sauces and salad dressings from the European and US markets (80). They found none exceeded tyramine 10 mg/kg.

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Fish

Fresh fish

Levels of both tyramine and histamine may be increased in poorly refrigerated produce. However, with fish spoilage it is notable that histamine can be greatly elevated without significant elevation of tyramine (137). Many regulations limit histamine, to between 50 (USA) and 200 mg/kg (EU). Histamine itself causes Scombroidosis (20, 138), see below. Freshness and low-temperature handling is everything, and quality control and screening of imported produce continues to be a powerful force for improving hygiene and handling world-wide (115, 139).

A recent review confirmed low tyramine levels in properly handled raw and processed seafood (138).

Fresh fish usually has 2 – 5 mg/kg tyramine (140). Whole and filleted trout kept on ice for up to 18 days, max at 18 days was 7 mg/kg (141, 142). Frozen fish 1 mg/kg (143).

Herring, fresh, stored on ice (i.e. ~ 2°C) < 5 mg/kg (144, 145). Storage conditions varied a little, but histamine reached 400 mg/kg whilst tyramine was low. After reaching a maximum of 100 mg/kg after seven days, tyramine then decreased on storage to 15 mg/kg at 15 days.

Chilled fresh and frozen or thawed salmon (140, 146) had a max of 40 mg/kg at end of shelf life.

Concerning histamine in fish, see (147).

Cured fish

Various types of fish (especially salmon) are 'cooked' using food acids (see also 'pickling'). The most widely known dish using this technique is Gravlax, gravad lax (and various other spellings and derivations) which originated in the Scandinavian countries and has been adopted in America, especially in Jewish culture where the name has transmuted to 'lox'. The data elsewhere in this monograph allow confidence that fresh hygienically prepared fish done in this manner would be expected to be completely safe. However, as with vegetables, deliberately fermented, or matured, product may develop significant tyramine concentrations.

Smoked fish

Smoked salmon (148) dry-salted, traditional smoking, sliced, vacuum-packed stored nine days at 4°C and 19 at 8°C contained no tyramine.

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Cold smoked salmon tyramine < 20 mg/kg (149).

Dried Fish

Dried salted Tuna roe, tyramine was 90 mg/kg (150).

Canned fish

Some canned samples reach tyramine 10 mg/kg, but that seems rare (151). Max 70 mg/kg (152). Histamine (some were > FDA limit of 50 mg/kg), one was 1,000 mg/kg of histamine.* see (153, 154).

*That level of histamine would likely precipitate 'scombroidosis' in someone on phenelzine.

Pickled fish

Pickled herring does not involve a fermentation process and such products are safe providing they are hygienically prepared from fresh fish. Modern food auditing processes controlling the hygiene of processing plants, and low temperature processing, suggests that all commercially available supplies are likely to be of good quality and therefore safe. As with vegetables (cf. sauekraut), product that has undergone a fermentation process is different, and can contain significant concentrations of tyramine, like the Strömming (herring) in Baltic countries, which is fermented. So, the Norwegians have their rakfisk (fermented fish), and the Swedish fermented herrings (Surströmming), Icelanders fermented shark (Hákarl or kæstur hákarl), and perhaps on the Kamchatka peninsula they fester something similar, perhaps an unmentionable part of a brown bear buried in a peat bog for months. There are no available tyramine data on these. But if you have read this far without learning already that they are obviously to be avoided then … .

Fish sauces

See 'Fermented Sauces' above.

Malaysian budu and cincalok

Malaysian local appetisers 'budu' and 'cincalok' (95) tyramine up to 450 mg/kg.

Pizza

It depends what you put on it! It should be clear from the data in this monograph that almost all commercial pizzas are highly likely to be safe, as found by Shulman (155). This is because they are most unlikely to use anything other than commercial processed cheese, or non-matured cheese types (e.g. mozzarella, which has no tyramine).

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Also, any salami type products on them are likely to be in small quantities, and also of the type that is low in tyramine. Pizza chains/franchises may change their cheese blend to stay abreast of cheese fashions, but for cost reasons are most unlikely to use large proportions of matured cheese that might have a higher tyramine content.

Gourmet pizzas may contain mature salami and cheese with higher tyramine concentrations, but the quantities are likely to be small so the total tyramine load is unlikely to be problematic. The data herein should allow a reasonable estimation of the total amount of tyramine. Sensible caution is therefore appropriate with some "gourmet" pizzas and with large servings of some "commercial" pizzas.

Vegetables and fruits

Vegetables generally have total BA concentrations of only a few mg/kg and tyramine levels of about 0.2 mg/kg with a maximum of 1 mg/kg (156), but can these increase a little with spoilage (see below re avocados). As stated in 'Key facts' in normal sized portions all these things are safe.

Plants do produce an extra-ordinary range of amines and psycho-active alkaloids, many are part of the ancient battle whereby plants manipulate the behaviour of animals and enhance their own survival (e.g. think of opiates, cannabis, tannins, nicotine, atropine, hyoscine, aperients & innumerable toxins). Many of these compounds are more common in a greater variety of plants than a casual reading of the literature would lead one to suppose. Their concentration varies greatly depending on many factors like plant variety, tissue type, stage of growth and attack by other organism etc.

Useful reviews are: (156-159), it has recently emerged that some of these compounds affect TAA receptors and TRP channels e.g. capsaicin, menthol (160).

Avocado and banana

There is one credible report of high BP after consumption of about six avocados, probably over-ripe (161). There are no recent data on Tyr levels. However, see below, it is possible for fruits to produce such amines and large quantities of rotten fruit (browned/blackened) may accumulate sufficient tyramine to cause a rise in BP. The fact that there have been no further reports in more than thirty years indicates it is pretty difficult to ingest risky amounts via fruits.

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Bananas can have significant dopamine, up to 400 mg/kg in the pulp, about 1,500 mg/kg in the skin (162), but probably little tyramine (159, 163). The first report of dopamine was in 1958 (164). Large amounts of banana (20 per day) may increase plasma dopamine concentrations (165). This may be via release of endogenous DA, and or via L-DOPA or other precursors or releasers. So, although DA cannot cross the blood brain barrier brain (or only to a limited extent (166)), plasma DA may be elevated, and raised peripheral DA may raise BP by vaso-constriction. As with all plants, concentrations will vary greatly according to variety, part of plant, stage of growth, maturation, ripeness etc. and it is clear concentrations are much higher in the skin (1,000 mg/kg) than the pulp (162), at only 2 mg/kg (167) and see (168-170).

Banana might possibly inhibit the adsorption of medicinal L-DOPA (171, 172). It is very unlikely that bananas in usual quantities would have any significant effect.

Paprika and green pepper appear to have higher tyramine contents 286 and 141.5 mg/kg of dry weight, respectively (157).

There is always something new. Ever heard of 'fermented minced pepper'. Well evidently it is enjoying rising popularity in China! It may well have slightly elevation tyramine levels (173), so do not eat it by the jar-full.

In summary, it would seem normal servings of fresh vegetables, fruits etc. are unlikely to have any serious adverse effects via histamine, tyramine or L-dopa (that includes broad-beans, aka fava beans, and possibly related species).

Nevertheless, interactions are sometimes noticeable and there is much yet to learn about the psycho-active contents of plant derived foods. One interesting recent reaction [personal communication] involved a reliably documented alteration of BP associated with consumption of quince paste, for which there would appear to be a possible explanation, since it has been claimed to contain a constituent that acts as a dopamine re-uptake inhibitor (174). This finding needs to be replicated, especially because the probity of much Chinese research is doubtful (175).

Spinach

Tyramine in spinach (176) was < 5 mg/kg, but histamine can be higher ~ 50 – 100 mg/kg.

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Fava/faba beans

Fava beans (*Vicia Faba*, aka broad beans) have tyramine at about 10 mg/kg (156), & L-DOPA, but at low concentrations, which is probably not sufficient to have any effect in normal portions. See 'L-DOPA'.

L-DOPA

Dopamine (DA) is present in many plants and plays a role in repelling pathogens. It is the precursor of the quinones that cause browning when they polymerise into melanin (e.g. bananas, avocados). Some legumes contain significant amounts of L-DOPA in some tissues, at some stages of growth, including *Vicia faba* L. varieties (aka fava beans, broad beans) and *Mucuna pruriens* (Cowhage, itching powder) (177-182). Varieties of these plants are being genetically engineered to try to find a suitable dietary source for L-DOPA because it may be better than pharmaceutical L-DOPA (better absorption, more stable plasma concentrations). Various preparations are being sold on the internet. A search for 'mucuna aphrodisiac' or 'mucuna parkinson' returns many thousands of hits.

Maximum concentrations of 10-20 mg/g (dry weight) have been found in *Vicia faba* (177), equivalent to a wet weight concentration of approximately 100 mg/kg. However, the edible beans are lower.

Since L-DOPA is a dopamine precursor, not a releaser, i.e. not an indirectly acting sympathomimetic like amphetamine is, it is likely to have an effect more analogous to L-tryptophan with MAOIs (i.e. moderate potentiation only). L-tryptophan does not cause serious problems with serotonin toxicity, and nor would one expect L-DOPA to do so with BP.

Despite the warnings on interactions with medicinal L-DOPA, early papers were, (183-185). The evidence for serious hypertension (see below for discussion) with L-DOPA and MAOIs seems inconclusive.

Such amounts of L-DOPA may potentiate or precipitate moderate BP increases, but, in my opinion, it is unlikely that a seriously risky BP elevation would result.

Pickling and preserving

Preservation, mostly of vegetables, using the acidic properties of natural acids, mostly acetic and lactic acid, is widespread and usually involves no fermentation, just the addition of vinegar (acetic acid), as in typical pickled onions. However, other pickled preparations involve a bacterial lactic acid fermentation process, such as

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sauerkraut and kimchi, see below. It is these fermentation processes which can give rise to small amounts of tyramine. Naturally occurring fermentation, without the use of starter cultures (see above) tends to produce more contaminant biogenic amines, including tyramine.

Olives, capers, caper berries

Preparation of olives may involve bacterial lactic acid fermentation, tyramine levels in olives, and capers are very low (186, 187).

Sauerkraut

Sauerkraut is made by lacto-fermentation, as are kimchi & traditional pickled cucumbers. These keep for several months, unrefrigerated.

Sauerkraut: review (101), more than 100 samples from 7 countries, almost all tyramine < 200 mg/kg, but a couple from Czech Rep. were 400 – 900 mg/kg.

Tyramine concentration was 50 mg/kg in one canned sauerkraut other samples < 12 mg/kg.

Korean 'kimchi' cabbage average tyramine 50 mg/kg, max 120 mg/kg (75).

Lavizzari (158, 159): Spinach tyramine 2 mg/kg. Histamine concentrations were 100 mg/kg.

Kosson (188) found insignificant levels of tyramine.

Chocolate

Chocolate sometimes does involve a short fermentation stage. Somewhat variable concentrations of amines have been reported, mostly very low, and inconsequential — unless *large* quantities are consumed (i.e. more than 100 grams).

A few recent papers have added data on dozens of samples of cacao powder, chocolate (white, milk, dark) and syrup, see especially (189, 190), none of which exceeded 35 mg/kg, most being < 10 mg/kg.

These other results are in the same range:

Pastore found 2 mg/kg for tyramine (191). Lavizzari (159) found concentrations of tyramine of 0.3 mg/kg. Baker (192), powdered cacoa: tyramine 3 mg/kg, chocolate < 1 mg/kg & Granvogl (193), Mayr (194), Baranowska (195), Spizzirri (196).

Health supplements

Such substances contain all sorts of crazy additives, many of them are potentially injurious, and most of them useless. They should list

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the ingredients, if they do not, then they should not be used. If they do, then do not use them if they contain tyramine at levels that would be injurious, i.e. more than 5-10 mg per portion or 'dose'.

Other non-serious interactions

Many plant derived substances (alkaloids), e.g. 'herbs' and 'foods' like coffee, and tea contain various compounds that act as 'drugs', stimulants like caffeine, 2-phenylethylamine, methylamine, trimethylamine (see Strolin Benedetti & Tipton (197)). These affect everyone but may have an exaggerated effect in those taking various sorts of antidepressant drugs, including MAOIs; they should be taken in moderation and avoided if they precipitate symptoms such as tremor, anxiety, jitteriness, palpitations, tachycardia, agitation, or poor sleep.

Some tyramine champions

One soy sauce clocked in at 6,000 mg/kg (88), does one smell a rat there?

An old cheddar cheese measurement from the 1950s 3,700 mg/kg (47).

An Italian goat cheese at ~ 2,000 mg/kg (198)

And, there is a French cheese called 'crotte du diable' (translates as 'Devil's turds'), and various rotten fish brews (best consumed on isolated Scandinavian mountain tops), that one presumes would be contestants, but I was unable to find any data. Would any lab technician be brave enough to endure them?

For an introduction to some other strong smelling foods see Andrew Zimmern:

http://www.openjourney.com/article/18-stinky-foods-around-the-world-41.html

Holidays

Some holiday destinations will require heightened awareness of food hygiene issues, in "Biogenic amine contents in selected Egyptian fermented foods as determined by ion-exchange chromatography" Rabie found levels of 2,000 mg/kg in cheese and fermented sausage (199), then there is fermented Yak milk (76), and Icelandic fish-dish called Hákarl (fermented shark meat).

Wine, spirits and beer

A meal without wine is like a day without sunshine.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

Anthelme Brillat-Savarin

Wine and beer in moderation (two drinks in 2 hours) are definitely safe (as far as tyramine is concerned). Modern hygienic production methods for beer have made tyramine concentrations > 10 mg/L rare (there is now extensive regulation and documentation of this, see below for details). Home-made wines or beers may be risky. Bottled beer is safe if pasteurised; a little caution is warranted with 'live' beers which may be available from 'boutique' producers. They can be distinguished by the sediment (of dead yeast) in the bottom and they are cloudy if shaken.

Modern commercial wines very rarely contain significant tyramine.

Tyramine in liquids taken on an empty stomach should be regarded as a special case, because tyramine will be absorbed much more rapidly (200, 201), so amounts of tyramine of one third of the figures given above may evoke a reaction. One small (330 ml) glass of some 'live' beers could, in *rare* instances, have about 10 mg of tyramine; this is sufficient to cause a reaction in a minority of people, when taken on an empty stomach, e.g. see (30, 202).

Wines

Here with a loaf of bread beneath the bough,
A flask of wine, a book of verse - and thou
Omar Khayyam

Wine does, if only rarely, contain significant concentrations of tyramine.

Recent major reviews have covered many hundreds of different wines of all types: almost all have had tyramine levels of less than < 5 mg/L (203-211).

Aged wines, all tyramine < 5 mg/L (212).

Thirty different wines, including aged fortified wines (Port and Madeira), max tyramine 5 mg/L (213). Wines 200 samples, histamine average 1.2 mg/L (214) and 300 samples max tyramine < 5 mg/L (215, 216).

USA wines, max tyramine 3 mg/L (207).

Marcobal, 61 different Spanish wines including aged Rioja Gran Reserva wines (217): Tyramine range 0–11.32 mg/L, Average 1.40 ± 2.35 mg/L. Only 34 of 61 wines had *detectable* tyramine.

However, Preti et al. found 8 of 60 (personnel communication) Italian wines tested recently had tyramine levels > 10 mg/L (218), none of these were chiantis!

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

The repetition of the notion that Chianti, uniquely amongst wines, contains significant concentrations of tyramine (63), illustrates, so it seems, how easy it is to be careless about the relevance and reliability of sources of information. The chianti error was countered long ago (219). The most likely explanation for these anomalies is that in the past many of these wines were made by farmers with little knowledge of wine or fermentation techniques. Hygiene practices were poor; it is only in the last 20 years or so that Italian winemaking has reached a modern standard, in most places.

Vinegars

Ordinary vinegars low tyramine, but: Chinese rice wine vinegar (old) 400 mg/L, Sherry vinegar 15 mg/L, Italian Balsamic ~ 15 mg/L (220).

Beers

Standards, and awareness of brewing hygiene issues, have increased since some of the older results, but caution is still warranted: it would seem likely that most, but not all, standard commercial and modern beers all over the world will be safe (< 10 mg/L) in moderation; some low volume 'artisan' and 'boutique' ones are a little more likely to be risky. Beers made using natural yeasts (spontaneous fermentation) rather than starter cultures, are more likely to have contaminants and therefore high tyramine. This is an observation echoed throughout this monograph with all types of 'fermentation', whether with cereals or sausages. Some examples are high enough to be risky, especially if beer is drunk on a more-or-less empty stomach, when it will be absorbed more rapidly.

It is established that the presence of tyramine is indicative of bacterial contamination and less than ideal hygiene practice.

A review by Kalac (221-223), "195 samples of bottled or canned beers were purchased from commercial outlets in Germany, Austria, Belgium, Bulgaria, Czech Republic, Denmark, Spain, France, Great Britain, Greece, The Netherlands, Ireland, Italy, Portugal, Switzerland, and the former Yugoslavia". They found a great majority were low (2 – 8 mg/L, mean 7), but a few are up to 30 – 50 mg/L, with a maximum of 70 mg/L.

Bunka more recently reviewed 114 samples of beer from 28 breweries in the Czech Republic which were "monitored at their purchase and at the end of their best-before period" (224). Tyramine was < 10mg/L in 51 samples, between 10 and 50mg/L in 21 samples and 100 mg/L in 5 samples.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

Pradenas et al. in Chile assayed over 100 samples and found 99% of 316 beer samples were no more than 2 mg/L, one was 6 mg/L (225).

Tang (226):18 beers all brewed in China, some European under licence, values mostly tyramine 3 – 5 (max 7) mg/L.

Spanish beer tyramine < 2 mg/L (227).

Spain, 17 samples mean tyramine 5 mg/kg; Spain, 55 samples mean 7 mg/L, max 47 mg/L. Europe 48 samples max 6 mg/L (228, 229).

16 European countries, 195 samples, mean tyramine 6.5 mg/L max 67.5 mg/L (230).

17 domestic Turkish and 13 imported beers (231), all were tyramine < 2 mg/L.

So, a great majority are low and safe, but if your favourite tipple is a 'micro-brewery', open fermented or 'live' or something exotic like Belgian lambic, watch it! Test it out very carefully before swigging too much!

Ken Shulman's group (232) looked at a total of **98 beer samples** (79 different brands of beer) in 1994:

> 'All of the bottled beers analysed had safe tyramine concentrations (< or = 10 mg/liter; range, 0 to 3.16 mg/liter) and, thus, do not require restriction in patients receiving MAOIs. Therefore, the consumption of canned or bottled beer, including dealcoholized beer, in moderation (fewer than four bottles or cans; 1.5 litres within a 4-hour period) appears to be safe and does not require restriction in patients receiving MAOIs. Only 4 of 98 beer samples studied were found to have a dangerous (> 10 mg/liter) tyramine concentration, one of which was the index beer. The tyramine concentration in these four beers ranged from 26.34 to 112.91 mg/liter. All four of these beers were tap beers produced by bottom fermentation (lagers) and brewed by a secondary fermentation process. … Therefore, to err on the side of caution, it is recommended that patients on irreversible MAOIs avoid beers on tap'.

This was an influential paper; subsequent knowledge suggests a slight modification of their conclusions.

Belgian beers especially can have high tyramine. Loret et al. (233), considered a large number of these Belgian beers: the types covered four different brewing processes; low or bottom fermentation (LF, 18 samples), top fermentation (TF, 36 samples), top fermentation followed by a secondary fermentation in bottle (TF+ BSF, 184 samples), and spontaneous fermentation (SF, 42 samples).

They found 21 samples out of 220 that exceeded 10 mg/L of either histamine or tyramine, these 21 had a mean tyramine of 28 mg/L, and the maximum was nearly 70 mg/L. They developed a "Beer biogenic amine index" (BAI) that would allow assessment of the quality of the production process. Since the work was financed in part by the Belgian Brewer Confederation we may assume they are

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

trying to improve things because of EC regulations and a recommended limit of tyramine 10 mg/L.

Belgian Lambic beer is an old style (see Wikipedia for information) allowed to spontaneously ferment with wild airborne yeasts and then aged for 1 – 3 years, breweries locate their open fermenters in well-ventilated attic roofs. The general category is spontaneously fermented beers (SF beers) which are obviously likely to have more tyramine (because they have more 'contaminant' organisms).

One more recent assay of SF Belgian beer found only 20 mg/L of tyramine, which may well reflect improved standards (233). Gueuze is an aged unflavoured Lambic style. This is a good illustration of why dirty farmhouse styles of anything are more likely to have contaminant strains that have decarboxylase activity, and thus potential for tyramine production, especially if a rat/sparrow/cockroach falls into the open fermenter.

MAOIs and scombroidosis (histamine fish poisoning)

The anti-tuberculosis drug isoniazid (INH) is closely related structurally and pharmacologically to phenelzine, but not related to tranylcypromine. INH is capable of inhibiting one of the other amine oxidase enzymes, the one which is largely responsible for breaking down histamine. The result of this is increased sensitivity to any histamine ingested in food by patients on INH and many histamine reactions have been described (234-241). The potency of phenelzine (but not TCP) for these effects is probably similar to isoniazid, and the blood and tissue concentrations reached in the system are also probably similar. However, there have been no reports of definite histamine reactions involving phenelzine: nevertheless, it is probable that phenelzine does increase people's sensitivity to histamine. The seminal early work by Blackwell and Marley is still well worth reading, and indeed, they presciently predicted sensitivity to histamine as discussed in this MS — they were indeed way ahead of their time (42).

Bearing in mind that foods that accumulate tyramine, like cheeses, may also have elevated histamine concentrations, this may be of relevance to patients taking phenelzine.

Symptoms of histamine poisoning are: lowered BP, headache, palpitations, skin flushing, nausea, vomiting, and pruritus (itching).

The symptoms of histamine poisoning relate especially to effects on blood vessels, cell permeability and smooth muscles, and include headache, nasal secretion, bronchospasm, tachycardia, extra-systoles,

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

hypotension, edema (eyelids), urticaria, pruritus, flushing and asthma (242, 243). Serum tryptase concentrations may help to distinguish allergic symptoms from scombroidosis (244).

It is inevitable that some instances of BA poisoning will exhibit mixed symptoms of both histamine and tyramine effects, especially in people taking hydrazine drugs like carbidopa, isoniazid and phenelzine, and as above, Blackwell and Marley discussed this, but it does not seem that anyone has read, or at least remembered, what they wrote — maybe we might stop a moment and raise our glasses for a toast in their memory.

Marley went on to write more seminal papers on MAOIs that are important vis-a-vis ST (245-250), those were also 'over-looked' by almost all writers: so raise your glass again.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

Part 2 Drug interactions

The place of MAOIs in treatment

> 'In questions of science, the authority of a thousand is not worth the humble reasoning of a single individual.'
> Galileo Galilei

A brief survey about the place of MAOIs in modern practice provides perspective and reveals the disproportionate influence on doctors' prescribing practices of 'promotion' in its various and often deceitful guises. The pressure to influence doctors to prescribe new drugs has been driven by pharmaceutical companies and has been hugely successful. It is a triumph of greed and profit, barely restrained by ethics. The commercialism and advertising that now dominate science, to such a disproportionate extent, are regarded by many as a great problem. This has been dubbed 'McScience' and it is the new reality, as the erstwhile Lancet editor warned us a decade ago (251, 252):

> 'Journals have devolved into information laundering operations for the pharmaceutical industry'.

The incredibly low rate of prescription of MAOIs is starkly incongruent with the fact that they are recommended and endorsed by many reviewers and in all recent guidelines about the treatment of depression (1, 54, 253-266).

Yet only a tiny fraction of specialists ever use MAOIs (54, 263, 267, 268), despite opinion and evidence of their superior effectiveness for various groups of patients (9, 261, 265, 269-272).

MAOIs: Interactions with other drugs

> Science must begin with myths, then progress to the criticism of myths.
> Karl Popper

Myth: MAOIs have many problematic interactions with other drugs.

Yet there are no pharmaco-kinetic interactions and just two pharmaco-dynamic interactions: SRIs and releasers.

SRIs are easy to identify and avoid. Releasers very rarely cause reactions sufficiently severe to be high risk.

And doctors have been convinced that is difficult to cope with? I hardly think so.

The requirement, a simple requirement, is to learn which drugs fall into those two categories. Then it is all plain sailing.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

It is helpful to understand why this text, and my review papers, contradict what is said in standard textbooks and other similar sources (e.g. Physicians' Desk Reference, British National Formulary, Australian Medicines Handbook etc.). First, many of them are just plain wrong. Second, such publications cover a wide field as concisely as possible and therefore abbreviate and generalise to an extent that does not allow detailed evaluations. For example, such sources lump all tricyclic antidepressants together as being contraindicated with MAOIs. Such texts have insufficient space to discuss more precise considerations detailed in review papers and in this monograph. The view that the average doctor cannot understand such subtleties may also be a factor.

MAOI interactions are now clearly understood***, they are reliably predictable, and they are straightforward to avoid. There is not room for a lengthy discussion here, but readers may note that I have published widely concerning both pharmaco-kinetic and pharmaco-dynamic interactions, and the cytochrome P-450 characteristics, of most psychotropic drugs. Consulted those papers if you wish to have more understanding of this subject. They provide the back-ground knowledge for understanding these interactions. See particularly my review, 'CNS toxicity involving methylene blue: the exemplar for understanding and predicting drug interactions that precipitate serotonin toxicity' (3), which is my most recent summary of what needs to be understood in order to be confident about avoiding ST.

*** As a matter of historical record and to recall the admonitions about learning from history — both the 1964 JAMA editorial (273), which used the word 'hysterical' (with which I agree) and Blackwell (44) opined that the American reaction of taking Parnate off the market (for six months in 1964— the British did not follow suite) was way 'over the top'. Blackwell pointed out that the 'cheese' reaction should have been anticipated from pre-existing research; and I have said the same about the imipramine/MAOI interaction (i.e. ST), it took about 30 years before that was properly understood. Psychiatrist have an appalling record as students of pharmacology, it still is, and was ever, thus. It is something about which psychiatrists should be profoundly ashamed. I think it is that poor knowledge, combined with a therapeutically pusillanimous attitude, that are largely responsible for the enduring negative/nervous attitude to MAOI use (its just 'too difficult' for most of them).

For other aspects of interactions, or rather, lack of them, see also: (1, 4-6, 15, 16, 274, 275).

Non-therapeutic/illicit drugs

This commentary deals with licit therapeutic drugs.

MAOIs (including moclobemide) combined with ecstasy (MDMA) caries a high risk of fatal ST.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

Those requiring information about non-therapeutic/illicit drugs are advised to be wary 1) there is a lot of mis-information in medical texts and on the net. Some interact potently with MAOIs, because many of them are potent releasers of serotonin, dopamine and or noradrenaline (276): e.g. the interaction of moclobemide and MDMA is predictably toxic (causing fatal ST) and has caused a number of tragedies (277, 278). Note that combinations of releasers with re-uptake inhibitors will result in diminished effects/efficacy: so, for example, SSRIs will diminish the effects of 3,4-methylenedioxy-methamphetamine (MDMA, ecstasy). For further explanation about this see my review (3).

The following papers contain information and further references about 'designer' and novel psychoactive substances (276, 279-282).

Medically, such possible interactions are only likely to be seen as presentations to emergency departments, and are unlikely to be relevant to usual therapeutic practice.

MAOIs are not 'dangerous'

It is common to hear and read of MAOIs being described as 'dangerous'. That is neither logical nor reasonable.

Being ill with unresolved or poorly treated depression is much more risky than taking MAOIs because not only is the life-time risk of death by suicide around 10%, but also the Standardised Mortality Ratio SMR (which includes death from other causes than just suicide, such as heart disease which is increased in those suffering depression) is as much as 10 – 30 times elevated (283-294).

The view has been well argued by the eminent medical historian, Edward Shorter, that the dangerousness idea was encouraged and spread by pharmaceutical companies extolling the virtues of newer drugs (295), and that necessarily involves exaggerating the disadvantages of previously existing drugs.

Tranylcypromine has no clinically relevant pharmaco-kinetic interactions and phenelzine has almost none, certainly none that are clinically significant (1), which makes them much better, certainly in this respect, than most of the SSRIs and many other 'new' drugs.

The potentially risky interactions with MAOIs are the pharmaco-dynamic ones, the more likely and serious being:

1. Serotonin syndrome, caused by SRIs + MAOIs

And the other, less-frequently

2. Blood pressure elevation, much less risky, caused by tyramine in food, or by the releasers like ephedrine.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

Interactions with SRI anti-depressant drugs and other SRIs

Any drug that works as a serotonin reuptake inhibitor (SRI), not just the SRI anti-depressant drugs, but including the SNRIs and a few other drugs that act as SRIs (even if not marketed as such) produces a high and predictable risk (possibly fatal) of ST, if combined with a usual *therapeutic* dose of an MAOI (which includes **reversible inhibitors of monoamine oxidase A (RIMAs**) like moclobemide (2, 274, 296, 297). ST is not an idiosyncratic interaction; it is a predictable dose-related toxic interaction.

Especially in the last 20 years or so ST has led to a number of deaths from ST, mostly entirely avoidable and many due solely to the ignorance of doctors about this interaction. A pressor response to excess tyramine has led to few, if any, deaths over this same period.

The category of serotonin reuptake inhibitor drugs includes:

1) All SRI and SNRI anti-depressant drugs**:** sertraline, fluoxetine, paroxetine, fluvoxamine, citalopram, escitalopram, vortioxetine, clomipramine and imipramine* and chlorpheniramine (aka chlorphenamine) and brompheniramine, or SNRIs: milnacipran, levomilnacipran, venlafaxine, desvenlafaxine, duloxetine or sibutramine.

* It is usually stated that all TCAs pose a risk, but that is definitely not correct, it is only clomipramine and imipramine that are sufficiently potent as serotonin reuptake inhibitors to precipitate ST; all other TCAs like nortriptyline, amitriptyline, trimipramine, dothiepin, doxepin, desipramine, protriptyline, are quite safe (as are selective NRIs like reboxetine and atomoxetine).

NB There have been one or two other 'odd' 'SRI' drugs like SNRI anti-depressant sibutramine (298, 299) that were (eventually) marketed for other indications (appetite suppressant), but sibutramine has been withdrawn world-wide (300, 301).
For a database of withdrawn drugs see (302)
http://cheminfo.charite.de/withdrawn/

The anti-histamines brompheniramine and chlorpheniramine (aka chlorphenamine), should be avoided because they have significant SRI potency (303-313). Other anti-histamines appear to be safe, but better SERT affinity data would be reassuring. NB the current generation anti-histamines do not cross the BBB, so cannot contribute to ST.

All of these old tricyclics came from the same pool and some were inappropriately classified as antidepressants, such as doxepin, and some inappropriately as antihistamines, e.g. chlorphenamine. Indeed, it would be logical, once more accurate data is available, to reassign them to different pharmacological groups based on their actual properties. Meanwhile, it is useful to remember that doxepin (classed as a TCA) is the most potent antihistamine currently on the world

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

market, and it definitely does not have any significant SERT affinity, and definitely does not cause significant ST.

2) Some narcotic analgesics, because some of them also act as SRIs: meperidine (aka pethidine) and tramadol (16) and less often used dextro-propoxyphene and dextro-methorphan. They are only weak SRIs, so therapeutic doses will rarely cause ST: it is usually only after larger and repeated doses that fatalities occur.

All non-narcotic analgesics are safe to take with MAOIs: aspirin and paracetamol and all the NSAIDs etc.

Releasers (indirectly acting sympatho-mimetics)

One or two recent papers about the mechanisms of action of MAOIs and amphetamine at the molecular level suggest why the combination of amphetamine (with MAOIs) is not unduly risky as has been (mis)stated for so long. Care and experience are required but it can be done safely although small increases in dose do sometimes seem to have disproportionate effects.

Amphetamine is a potent DA and NA releaser (in former terminology, an ISA) at low nano-molar (10^{-9}) concentrations. There is still uncertainty about its exact mechanisms of action and just how it interacts with the monoamine transporters etc. It acts as a competitive inhibitor (for NAT & DAT) and has actions in the pre-synaptic cytoplasm, at the vesicular monoamine transporter (VMAT) and TAR1 receptors. The latest understanding of this is complex and beyond the scope of this review. Further details are in: (314, 315). Those using these combinations may wish to study these references to understand more about 'non-exocytotic release' that does not require any neuronal activity (viz. nerve impulse) to trigger it, and how they inhibit reuptake in a competitive manner and more.

Unsurprisingly, considering the multiple sites at which drugs classed as amphetamines affect the neurotransmitter systems, there are marked differences between closely related drugs: for instance, methylphenidate (which is classified as an amphetamine) seems to be mainly a DA re-uptake inhibitor, and not a releaser. It produces no risk of ST, nor a pressor response.

As Paracelsus stated '*the dose makes the poison*' and that may be particularly applicable to amphetamine. Releasers are capable of increasing intra-synaptic transmitter concentrations by more than 1,000-fold, compared to a maximum closer to 10-fold with reuptake

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

inhibitors (315) — cf. see (6) re such mechanisms of interactions involving RIs, releasers and MAOIs.

Amphetamine causes NA increases of a lesser magnitude (400–450% of baseline) compared to dopamine (700–1500% of baseline). This suggests that used carefully the risk of precipitating hypertension is low (as practical experience indicates, see Israel for a recent report and review (316)). The advent of lisdexamfetamine may now add another layer of safety because its slow conversion to the active form (d-amphetamine) occurs in red blood cells by rate-limited enzymatic hydrolysis. This means the time to T_{max} is rather longer and peak levels are lower, about half (317). It also has a low potential for cytochrome P450 interactions (318, 319). Not only that, but also the inter- and intra-subject plasma levels are much less variable which produces a 'smoother' and more predictable response (320). An unusual example of the usefulness of a pro-drug. It is to be expected that this combination (with MAOIs) will be even safer than previous preparations (316, 318, 321-325).

Ephedrine is rather less potent than amphetamine (326-328). Pseudoephedrine is much less potent than ephedrine.

Pseudoephedrine and Ephedrine, the archetypal drugs of concern, are still available for general use in some countries, whereas in most they have been replaced by oxymetazoline (which does not interact with MAOIs). Previously they were components of cough and cold remedies. Reactions are unlikely to be severe or dangerous unless large (oral) doses are used (that usually means an overdose).

Adrenaline (epinephrine) and noradrenaline (norepinephrine) are, obviously, (because they are the body's neurotransmitters that act at these receptors) direct post-synaptic agonists and therefore do not cause any problematic interaction with MAOIs. Equivocation about that has been evinced repeatedly over the years in most standard texts and has caused mistreatment of patients e.g. (329), yet the lack of an interaction was established at the dawn of modern pharmacology by researchers whose names are prominent in history (Gaddum and Brodie, among others), early papers being (330-332). That work has been forgotten. It is TCAs that have a more pronounced interaction with adrenaline, ironically I cannot recall anyone getting too worried about that.

There is now quite a lot of accumulated experience of the concurrent administration of MAOIs and amphetamine for

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

therapeutic purposes in depression. It is safe when done carefully. Early concerns about frequent hypertension have not materialized and recent clinical reviews indicate judicious use is safe (333, 334). Since amphetamine is substantially more potent than ephedrine it would seem, by extension, that concerns over this drug may also have been be over-rated. If taken in supra-therapeutic doses or overdose the situation may be different.

Traditionally concern about interactions has centered around cough and cold remedies and nasal decongestants because of early confused reports in the 1960s, e.g. (335, 336) and because they may contain both SRIs (e.g. chlorpheniramine (aka chlorphenamine), dextromethorphan and releasers like ephedrine). Note that until the 1990s, and in some reports beyond, there was a failure to understand the toxidromic distinction between a risky pressor response and ST. That failure has caused much confusion. The unrecognised irony was, until my 1998 review, it was not recognised that the chlorphenamine component of such over-the-counter (OTC) remedies is an SRI, and therefore a potential problem for precipitating ST. Indeed, as I noted, chlorphenamine was a possible, but unrecognized, contributor to the death of poor Libby Zion in a much, but inaccurately, commented on case (337-339).

One may also note here another classic case of pharmacological misunderstanding. It did not attain notoriety, the doctors were lucky because the patient was on a sub-therapeutic dose of phenelzine (only 15 mg daily) and therefore did not get ST (329). These doctors misguidedly eschewed adrenaline to treat an anaphylactic reaction because their patient was on phenelzine, so instead gave intravenous chlorphenamine. In view of the text above no further explanation of this, fortunately comical, error should be required.

Chlorphenamine, in the usually recommended doses of 10 – 20 mg IV, and up to 40 mg in 24 hrs., is almost certain to attain sufficient blockade of SERT to precipitate ST in combination with MAOIs. The warning with it, below, is a good example of the kind of unhelpful mis-information that is still in 'official' texts:

> 'The anticholinergic properties of chlorphenamine are intensified by monoamine oxidase inhibitors (MAOIs). Chlorphenamine injection is therefore contraindicated in patients who have been treated with MAOIs within the last fourteen days.'

Incredibly, not a word about SERT inhibition and the probability of ST. Incidentally, I wrote to the regulatory authorities about that years ago. My communication was ignored. Some culpability there one might think.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

Typical constituents of available cough and cold remedies and nasal decongestants were: phenylephrine, pseudoephedrine, both weak releasers and now mostly replaced, or phenylpropanolamine now completely withdrawn. The usual constituents of cough and cold remedies now are the MAOI-safe alternatives: oxymetazoline, xylometazoline and ipratropium bromide.

Herbal preparations: ephedrine is in various plant species, e.g. Ephedra sinica (Ma Huang).

As Rothman states, 'Historically, it has been difficult to distinguish whether drugs act as reuptake inhibitors or substrate-type releasers using simple test tube assays.' But it seems now established that amphetamine is a moderately potent NE and DA releaser, but a weak 5-HT releaser (326-328).

Therefore, over-the-counter drugs are hardly a problem now, because even pseudoephedrine has been taken off the market (at least, in many western countries).

The commonest 'non-releaser' nasal decongestant is oxymetazoline, which is an adrenergic alpha 2 agonist: it has no interaction with MAOIs and is not a problem.

Directly acting agonists, such as midodrine and adrenaline itself, are not a problem with MAOIs, because there is no potentiation, something that was established over half a century ago.

In summary: releasers are almost a problem of the past, and in any case are unlikely to cause severe reactions in normal moderate therapeutic use.

Anti-psychotic drugs

All available anti-psychotic drugs have, until recently, been safe with MAOIs. However, one newer so-called atypical, ziprasidone (Zeldox), possess SRI potency and has been implicated in a case of definite ST in combination with an MAOI (340), it is therefore contra-indicated with MAOIs.

Triptans

There is no risk of ST with triptans. The FDA have issued various misconceived warnings, particularly about triptans and serotonin toxicity: see Gillman (4). There has been no subsequent rebuttal of the conclusions in that review, that there is no risk of ST with triptans, either by the FDA or by anyone else. Other reviews and comments concur with my conclusion (341-344).

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

Anaesthesia

Myth: One cannot give an anaesthetic without ceasing MAOIs first.

The main issue in most operations, and post-operative periods, is the avoidance of analgesics that act as SRIs, viz. meperidine (pethidine), tramadol, dextromephorphan and pentazocine. Other opioids like codeine, oxycodone, morphine, fentanyl, are safe (see (16)).

The idea that an anaesthetic cannot be given without first ceasing MAOIs is yet another of the deeply embedded and ill-founded concerns that one encounters. Sadly, it is not inconsequential, because poorly informed careless surgeons (some of whom would struggle to spell 'pharmacology') may tell patients due for elective surgery to cease treatment, sometimes without being aware of their history. I have had experience of suicides from relapse of depression as a direct result of such ill-advised cessation of treatment. Therefore, my disparaging view of those surgeons who are too ignorant and arrogant to ask advice, or even inform the prescribing specialist that they have ceased the treatment, will be understandable to some.

In 'uncomplicated' anaesthesia, apart from avoiding any use of narcotic analgesics with SRI potency, there are no major problems or interactions. The preponderance of published opinion is, fortunately, lining up behind that view (345-352).

For 'major' operations that might require treatment to raise or lower blood pressure there are some minor adjustments of dosage and agents that may be required, but there are no major obstacles. For instance, the hypotensive effect of MAOIs may mean that intra-operative hypotensive measures may be potentiated, and accordingly doses of such drugs may need to be lower. On the other hand, if vasopressor agents are required then directly acting alpha agonists may have their effects *slightly* potentiated, that means norepinephrine, epinephrine and phenylephrine doses may need to be slightly lower when used in patients on MAOIs. Since ephedrine has releaser potency it is best avoided.

Stopping and swapping, easier than often supposed

On ceasing SRI-type antidepressants to start MAOIs, washout intervals varying between one and five weeks may be required. No washout is needed for non-SRI-type drugs. The rule of thumb is to allow 5 half-lives to elapse*, which is about one week for many of these drugs).

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

See, for a table of half-lives: http://www.health.harvard.edu/diseases-and-conditions/going-off-antidepressants

No washout is required for TCAs (other than clomipramine and imipramine), or mirtazapine, mianserin, bupropion, trazodone, reboxetine or atomoxetine, because they are safe taken together with MAOIs (i.e. anything at all is safe, except an SRI).

*Fluoxetine (via its metabolite norfluoxetine) has an elimination half-life in some people of up to two weeks (so it can take up to 10 weeks to get out of the system).
In practice 5 half-lives is a conservative approach. Most drugs will have lost sufficient SRI activity after two half-lives to allow cautious introduction of an MAOI- providing the patient can be observed for early signs of serotonergic over-activity.
Such signs are: 1) specific; tremor, hyperreflexia and clonus; less specific; GI overactivity, mydriasis, sweating, anxiety, restlessness, overactivity.
Should such symptoms be apparent it is simple enough to withhold the MAOI for another day or two and then try again. ST is a dose-related phenomenon and the emergence of more pronounced serotonin-related side effects is not a cause for immediate panic.

It is commonly thought and stated that it is problematic to change from one drug to another when one of them is an MAOI. In practice this is not a difficulty, once it is appreciated that almost anything, except an SRI, can be safely co-administered. The TCA nortriptyline is probably the best and most flexible candidate to fulfill a 'bridging' role because of its favourable pharmacological characteristics (no active metabolites, minimal pharmaco-kinetic interaction potential, medium length of half-life, mild sedative and low anti-muscarinic potency).

For instance, if one is changing between an MAOI and venlafaxine, which can have quite marked withdrawal symptoms, co-administering nortriptyline prior to reducing or ceasing the venlafaxine can both reduce withdrawal symptoms and act as a 'bridge' prior to the initiation of the MAOI. Exactly the same process works in reverse where nortriptyline can be added to a pre-existing MAOI, the MAOI is then stopped and most subsequent treatments can then be initiated with ease.

*One could use mirtazapine, doxepin, amitriptyline, quetiapine, (but not ziprasidone), mood stabilizers: in short, anything that is not an SRI. How difficult is that!

Swapping from one MAOI to another MAOI

The requirement or desire to swap from one MAOI to another MAOI is something that will be a rare occurrence. Furthermore, it will be an urgent need even more rarely. It may be indicated, for instance because of the excessive weight gain, sexual dysfunction, or oedema, that occur with phenelzine. Because opinion exists in the

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literature suggesting dove-tailing, or a direct swap, is a potentially risky thing to do, some discussion about this is educative.

Insofar as I have been able to trace the original texts which postulate these sorts of dangers I have one comment to make. Some are written by clinicians who have an incomplete understanding of pharmacology, or toxicology, and the contain errors of fact. Such texts are often books, most of which are not peer reviewed.

First, there is no known mechanism of interaction that would cause a problem. Neither is there a basis for postulating a pharmaco-kinetic interaction, and since both drugs have the same mechanism of action. Nor is there a basis for a major pharmaco-dynamic interaction. Which leaves a mystery, or possibly a phantom?

Second, my extensive experience analysing hundreds of case reports of ST illustrates clearly that the overwhelming majority of case reports are misleading*, and they often involve supposed interactions that have no known basis, in fact or theory. To make decisions based on such reports has repeatedly proved to be inappropriate and the resultant actions have in some cases had serious negative consequences.

*This is why many reputable journals decline to publish case reports (275).

The literature is replete with inappropriate and groundless injunctions against a host of perfectly safe drug combinations (see my other papers for a detailed analysis of this topic in relation to ST) and various 'official' bodies like the WHO and the FDA have been repeatedly guilty of issuing such scientifically groundless injunctions: recent examples are warnings about 'serotonergic' drugs precipitating ST if combined with the anti-emetic 5-HT3 antagonists, and about ST with Triptans. Such 'cry-wolf' warnings are time-wasting, and confuse and misdirect practicing clinicians. So, adopting the careful conservative approach is not always the 'win-win' scenario that such cautious analysts suppose it to be.

In routine clinical practice the maxim 'start low and go slow' is wisely adhered to. When a changeover is being considered, or is indicated, in a patient who is *severely* ill, and in danger because of that, a degree of risk, imagined or real, is acceptable. In less urgent circumstances the patient and clinician are usually well advised to opt for a cautious approach.

In more than 50 years of MAOI use there are only a few reports of supposed difficulties that are non-specific and not indicative of a cause-effect relationship involving an MAOI-MAOI interaction (353-357). It is notable that of these incomplete and unconvincing reports, one suggests subarachnoid haemorrhage and another

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serotonin toxicity. Clearly, it is unlikely that both of these represent a cause-effect interaction, because the required mechanism is quite different for each of them. The most parsimonious explanation is that neither of them represent a cause-effect relationship between the changing drug regime and the outcome reported. As with so many case reports these ones also contain insufficient information to draw reliable conclusions.

It is well recognised that abrupt cessation of antihypertensive treatment can cause rebound hypertension; indeed, this is a not uncommon presentation in emergency departments. It is forgotten that MAOIs are anti-hypertensive drugs, and, as I have reviewed elsewhere, were indeed used for the treatment of hypertension in the 1960s and 1970s. I have certainly seen patients who have developed high blood pressure when well-meaning primary care physicians have stopped the 'dangerous-old-antidepressants-we-don't-use-anymore' that the (doddery old) specialist has been giving because he does not know about the wonderful new drugs we now have (that the young lady drug rep in the short skirt who took me to lunch told me all about).

Furthermore, I have seen patients on long-term antidepressant MAOI treatment who have clearly developed idiopathic hypertension during the course of that treatment, which was 'disguised' by the MAOI. These patients then had substantial rises in blood pressure on cessation of the MAOI. Indeed, one of them actually had a small CVA whilst waiting for an appointment to see me, to decide on future treatment. The primary care doctor had already (unilaterally) instructed her to cease the tablets prior to the appointment with me. If that patient had already restarted another MAOI then where would the blame for her CVA have been laid?

The following are all the relevant contributions that I am aware of, in the published literature (353-363): re Torre et al. see 'case 2'. None of them are very helpful, nor do they provide a substantive basis for prohibition of a direct swap-over of one MAOI to another MAOI. One paper reports a small series of 8 cases where it was accomplished without a problem (364). I have personally done it without any problem, but only on a couple of occasions, as have associates and various people who have been in contact via my web site.

Opinion: if there is *good reason* to swap rapidly***, do it, because there is 1) no theoretical basis to suggest it might be contra-indicated, and 2) existing reports do not constitute evidence to the contrary, and 3) it has clearly been done many times without any problem

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***For example I remember a patient who had failed to improve with a long course of ECT, which had involved a long stay in hospital 1000 km away from home, whom had started phenelzine and was experiencing rapid weight gain and massively swollen the legs, remained suicidal, but dreaded a return to hospital. A direct swap to Parnate was successful and uneventful and led to great improvement.

MAOIs: Miscellaneous observations

NRIs and reducing tyramine sensitivity

Myth: One cannot combine MAOIs with TCAs.

Attenuation of the pressor response to tyramine was demonstrated long ago by the renowned pharmacologist Bernard Brodie. There is a sound pharmacological basis for the proposition that TCAs, by virtue of their NRI potency, attenuate the 'cheese effect' (365-370).

I assembled and explained the evidence for this in my TCA review (5) which concluded that those NRIs with a *high* affinity for the NAT (viz. reboxetine, desipramine, oxyprotaline, protriptyline and nortriptyline) have all been demonstrated to block the pressor response to tyramine almost completely (367, 371-376), even when it has been potentiated in the presence of MAOIs (377-379). The early demonstrations of NRI attenuation of the pressor response to tyramine go back a long way, past learning seems to have been lost for a long time (365, 366). NB Both those last 2 references are from the lab of the famous pharmacologist Bernard Brodie whose early papers are worth studying.

This leads to the confident conclusion about an old and bitter-sweet irony: combinations of (non-serotonergic) TCAs or NRIs (e.g. reboxetine etc.) with MAOIs are not risky, they actually make MAOIs safer, not more dangerous, by attenuating, or completely blocking, the pressor response to tyramine, or any other NA releaser (ISA).

If a patient is more than usually tyramine sensitive, they will become less so if a potent NRI like nortriptyline is added to the regime: the greater the dose the greater the attenuation of the pressor response. That is not just a 'theory', it is pharmacological fact.

Therapeutic hypotensive effect of MAOIs

Myth: MAOIs cause hypertension and should not be given to hypertensive patients.

MAOIs lower blood pressure: However, that MAOIs raise blood pressure is a widespread misconception, and one of the commonest incorrect statements you will see. It is incontrovertibly incorrect: it is

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only the interaction with releasers like tyramine that produces (a modest degree of) hypertension.

In the 1960s MAOIs were used to treat hypertension, until better drugs were found (380-382), and indeed using MAOIs for those suffering both depression and hypertension works very well.

The still repeated, but incorrect, prohibition about giving MAOIs to patients with pre-existing hypertension is thus another example of ignorance about pharmacology. Again, the basis on which this opinion has insinuated itself into the literature is impossible to pin down. It just appeared and was unthinkingly repeated by the pharmacologically ignorant presumably because it sounds sensible and responsible. The post 'Parnate-withdrawal' hysteria (1964) was fertile ground for such admonitions. Having been repeated so often it became 'received clinical wisdom', and even 'expert opinion', which is a capricious beast to be regarded with circumspection.

'Spontaneous' hypertensive episodes

One occasionally sees patients who do get brief episodes of hypertension (but not hypertensive emergencies) — I estimate between 1% - 5% of all MAOI takers — lasting a couple of hours, most often following the second dose of the daily regime of MAOI. There are a few reports in the literature (383-386). In my experience this usually gets less over a few weeks. If such elevations are problematically high, symptomatic, or enduring they will be controlled by giving propranolol with the MAOI dose, that also helps reduce exercise-induced postural hypotension by antagonising the noradrenaline beta-receptor-mediated vaso-dilation (in muscle vasculature).

However, there may also be another (presumably very small) group of patients in whom such elevations are related to occult phaeochromocytoma, and I have encountered such a case and one or two cases have been reported in the literature (387, 388). If such elevations are occurring outside of the 1 - 4 hr. post-dose 'window' then it is suggested that investigations for occult phaeochromocytoma, such as a high-resolution scan of the adrenals, should be undertaken to try to rule out a small adrenal tumour. MAOIs will magnify the pressor effect of even a small tumour.

Hypertensive urgencies and emergencies due to tyramine and the occurrence of subarachnoid haemorrhage

Deaths from tyramine/MAOI induced hypertension are *extremely* rare. Indeed, there have been no deaths from MAOI induced

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hypertension reported in the medical literature for decades. When De Villiers (389) reviewed this in the UK at the time Parnate was withdrawn in the USA (1964) he noted that of 21,582 treated with MAOIs (between 1960 and 1964), 2% developed headache, 0.27% had the 'hypertensive syndrome'. Fourteen deaths were reported in Great Britain out of an estimated one and a half million patients treated since the introduction of the drugs in 1960. The estimated risk for a patient treated with tranylcypromine was: for headache 2%; for hypertensive crises 0.5% and for death 0.001%. Note that this was when foods had much higher tyramine levels and *before* tyramine-restricted diets and an understanding of the pressor response.

If one takes into account the reduction of tyramine in all foods these days and the better dietary advice now issued, then the incidence of *serious* hypertensive events is now likely to be exceedingly low. Indeed, it is so low that it may be hard to distinguish from the background rate of spontaneously occurring subarachnoid haemorrhage in the general population.

The role of transient episodes of hypertension in the precipitation of subarachnoid haemorrhage has probably been over-estimated. Large numbers of patients are walking around with BPs well in excess of 200 mm/Hg with no (short term) increase in subarachnoid haemorrhage (or cardiac failure) risk: this view is supported by a 2016 paper reviewing 58,000 cases (390). This shows that the *acute* risk of BPs in the range 180-220 is immeasurably low even in a sample as large as 58,000.

Deaths from MAOI induced hypertension can therefore be inferred to be rarer than fatal reactions to various modern drugs. For example, SSRIs contribute to many deaths from **gastro-intestinal (GI)** bleeding. There is a significantly increased risk of GI bleeding related to SSRIs and the overall mortality rate from GI bleeds is still > 5% (391). The evidence that SSRIs contribute to increasing the frequency of bleeds is strong (392-398). So a GI bleed has a 1/20 risk of death and a serious hypertensive episode more like a 1/1000 risk. It is quite an irony that an SSRI side effect that most doctors do not even know about, or think about, may well cause far more deaths than the feared 'hypertensive crisis'. As they say '*what the eye does not see the heart does not grieve over*'.

That hypertensive deaths due to MAOIs are extremely rare should not be surprising as there are so many other things that frequently raise the blood pressure considerably higher than the majority of hypertensive episodes related to tyramine intake.

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Many physical activities, both indoors and out of doors, raise blood pressure as much and more. Healthy vigorous exercise will increase systolic blood pressure to 200 mmHg within five minutes where it will remain throughout the duration of the exercise, think about the craze for marathon running! Recent studies involved >1000 participants on whom blood pressure data were gathered during exercise: the average BP was 200 mmHg, maximum 290 mmHg (399-401).

Weight lifting, for instance, raises BP as high as 450 mmHg and readings of 300 or more are routine (402, 403).

It is important to maintain perspective on the issue of acute BP elevation (which is an irrational over-concern with many doctors).

The evidence suggests that very large increases of BP rarely precipitate subarachnoid haemorrhage, which many occur 'spontaneously' or with short and modest BP increases associated with, for instance, defecation (404).

This indicates the major factor determining a subarachnoid haemorrhage is a systemic vulnerability. Pressor events from many causes/activities, including tyramine ingestion, are only one factor and are somewhat indirectly related to any particular subarachnoid haemorrhage event.

Medical treatment of hypertension resulting from tyramine ingestion

If excessive tyramine is ingested the blood pressure starts to increase from about half an hour after ingestion (sooner for liquids on an empty stomach), and remains elevated for 1 – 2 hours: the magnitude and duration of that elevation is dose related, so unless a large amount of tyramine has been ingested (50 – 100 mg) the reaction will be short-lived (about one hour).

Current evidence clearly indicates that elevated BP without signs or symptoms of end-organ damage does not require, and should not be given, urgent treatment. This is because hasty and inexpert BP reduction may well do more harm than good (sub-lingual nifedipine is strongly contra-indicated*, see below).

A question, which cannot be answered with certainty, is whether catecholamine-induced hypertensive urgencies or emergencies are optimally treated in the same way as the more common event of hypertensive urgencies in subjects previously known to be hypertensive. The tyramine reaction is one example of catecholamine-induced hypertensive urgencies, others being the ingestion of amphetamine ('ice'), clonidine withdrawal, and phaeochromocytoma. They probably are comparable.

An SBP of 180 mmHg or more, sustained over 3 measurements in 10 minutes or so, performed in a calm setting with an accurate sphygmomanometer is now referred to as a 'hypertensive urgency'. Only if 'end organ' dysfunction is present it is called a 'hypertensive emergency'. End organ dysfunction is uncommon unless DBP is greater than 130 mmHg (405).

In hypertensive urgencies the treatment aim is to reduce BP slowly over 24 – 48 hrs. Since tyramine reactions are self-limiting over 2 – 4 hrs., or rather less with present, typically smaller, tyramine ingestions, it is clear they will *very rarely* require intervention. The exception to this might be when a large (> 100 mg) 'deliberate' tyramine ingestion has occurred and SBP is in excess of 220/130 mm/Hg.

Rapid reduction of hypertension (i.e. within 2 – 4 hours) carries a serious risk of catastrophic adverse effects (405-408) and such treatment is probably inadvisable, even if initiated in a specialist hospital setting.

Several of these recent reviews about hypertensive urgencies make very strong statements about premature treatment and about excessively rapid reductions of blood pressure.

> Flanigan: "Often the urgency is more in the mind of the treating physician than in the body of the patient … The compulsive need to treat reaches the pathological in some physicians, especially during the early years in their careers".
> Marik: "Rapid reduction of BP may be associated with significant morbidity … causing ischemia and infarction. it must be lowered in a slow and controlled fashion [over 24 – 48 hrs.] to prevent organ hypoperfusion."
> *Sub-lingual nifedipine is very strongly contra-indicated (408-411). It can result in uncontrollable hypotension and hypo-perfusion which may cause stroke or sudden permanent blindness. Indeed some experts have suggested instant/rapid-release formulations of nifedipine should be prohibited (412, 413) and that it should never be given to patients to self-administer.

Pain and anxiety exacerbate hypertension, so remaining calm and using a benzodiazepine, which will lower BP safely and to a significant and sufficient extent (414-417), is probably the most useful and safe *initial* step. As the above text suggests it is most unlikely that urgent hospital and specialist assessment will be required, unless a very large ingestion of tyramine is suspected (nowadays that would almost have to be 'deliberate'), and observation and BP monitoring shows BP increasing beyond 220 mm/Hg or so over a prolonged time (2 hours), or end organ damage.

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A great majority of BP elevations nowadays are going to be mild, from relatively small amounts of tyramine, and will last only an hour or so and require no intervention.

Ceasing Treatment

When MAOIs are ceased, precautions about diet and possible interacting drugs are advisable for four weeks after cessation, especially when starting SRI-type drugs. When SRI-type drugs are being ceased to start MAOIs, five half-lives of the relevant drug ideally should be allowed (various safe bridging strategies are available (see above), but a period of 3 half-lives is often sufficient if the MAOI is being started at a low dose, as is usually advisable.

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In view of the above it is appropriate to consider this monograph as 'peer reviewed'.

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

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Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

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Address for correspondence. Dr Ken Gillman: kg@matilda.net.au