

# Monoamine Oxidase Inhibitors (MAOI), Dietary Restrictions, Tyramine, Cheese and Drug Interactions

Dr P Ken Gillman V2.2.1 Jan 2011

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## Monoamine Oxidase Inhibitors, Dietary Tyramine and Drug Interactions

### Summary

#### Key facts

- This review summarises more recent and original scientific research papers about tyramine than any previously existing publication
- For people who already follow healthy eating (and drinking) amounts and patterns a low tyramine diet involves very few, if any, changes
- Only those foods that are past their shelf-life or 'off', or those prepared using maturation and 'fermenting' techniques, can *sometimes* have high tyramine
- The possible increased blood pressure reaction that can sometimes result from excess tyramine ingestion is proportional to the amount of the tyramine-containing food eaten
- There is almost no food or drink that is so strong (i.e. high in tyramine) that a small amount (i.e. 50 grams or ml [or less]) is *likely* to cause a serious or risky degree of hypertension
- Modern cheese is safe (in healthy-sized portions) but some mature or aged cheeses can sometimes have higher tyramine concentrations, so care and awareness is needed
- If a reaction ever did occur, and provided you attend hospital if and when you get symptoms, the chance of coming to harm is very remote
- The symptoms of a reaction are: a thumping forceful heartbeat (usually a **slower** than normal pulse rate), paleness (pallor), rapid onset severe headache, tightness in the chest. Pulse may drop as low as 40 beats per minute
- The risk of harm from blood pressure reactions with foods and MAOIs has previously been exaggerated
- Remind your doctors to check the compatibility of any medications they recommended you to take, also check the info in this monograph yourself.
- There are few over-the-counter ('OTC', non-doctor script) drugs that are a problem, because the pseudo-ephedrine type drugs (with intrinsic sympathomimetic activity [ISA]) have been taken off the market (in many western countries). However, any ISA (see below) may be risky.

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## General summary

Interactions between **monoamine oxidase inhibitors (MAOIs)** and other drugs are not a difficult problem, something that many doctors unfamiliar with these drugs have been led to believe. These interactions are now understood much more clearly: the author has published various scientific papers relevant to this topic and is also an internationally recognised expert on one special aspect of this, namely **serotonin toxicity (ST)** aka ‘serotonin syndrome’ (see especially (1-7)).

These interactions are neither frequent nor difficult to deal with; contrary to the impression generated by many standard textbooks. From the author’s long experience problems with MAOIs are less common than with some SSRIs, especially fluoxetine, which has multiple potentially problematic interactions and yet is still widely used (8). Also, problematic side effects are usually less with MAOIs than with SSRIs. Standard texts cover a huge spectrum of possible issues so, perforce, contain abbreviated and incomplete information that can cause confusion for some readers because it appears to contradict the contents of specialist texts and this monograph. The details and original references here will help to clarify these issues.

There is now much more quality data on the tyramine levels in foods, and also on how much tyramine is likely to constitute a problem. Some previous opinions and advice have been based on old, sometimes inaccurate, data and have been over-extrapolated from minimal information. This monograph surveys more original data on tyramine than any paper previously published. There are over 120 new references, mostly recent, that have never been considered before.

**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 the technically correct form.

So, if you live in a non-metric area, then get smart and think and work metric: it is unhelpful, illogical and confusing to work in standard servings/standard drinks or oz./pints. Many scientific papers from the USA 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 I am one meter 32.9 inches tall. Such practices are incorrect, illogical and ultimately dangerous, to people’s lives, as well as to spacecraft. This practice continues despite the ‘Mars Climate Orbiter’ spacecraft disaster which was due

to just such a mistake. Lockheed Martin used the non-SI units of pound-seconds (lbf-s), NASA use the metric (SI) units of Newton-seconds (N-s). As a direct result of that the MCO crashed into Mars (9). So, 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-unite-the-world.html>

Although a small proportion of people may get a significant blood pressure increase with only 10 mg of tyramine the majority of people need to have 50 mg or more (in a meal) to get a *serious* blood pressure increase (i.e. systolic blood pressure [SBP] > 220 mm Hg). For a detailed analysis of the evidence relating to tyramine dose and blood pressure see (1).

It is easy to work out how much tyramine is in 10 or 100 g/ml of any of these foods. Learn what 10 and 100 g looks like, and what sensible food portion sizes are: if you eat 1 kg beef steaks, or half a kilo of cheese, chocolate etc. then you will need to adjust to avoid trouble (and to become healthy). Some people (and if your BMI is more than 26 that may mean you) will probably benefit by consulting a dietician for explanations and education about how to eat sensibly. BMI (body mass index) is weight in kg divided by height in meters squared. i.e. for an average man =  $70 \text{ (kg)} / 1.7 \text{ (m)}^2$ ; or  $70 / 2.89 = 24.22$  Also see website information like

<http://www.win.niddk.nih.gov/publications/PDFs/justenough.pdf>

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

This is because healthy amounts of cheese are around 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 (i.e. 25 mg in 100 g = 250 mg/kg). So a 25 gram portion contains only 6 mg of tyramine and that is very unlikely to cause any measureable blood pressure increase at all in anyone. Matured cheeses contain 2-3.5 g of salt per 100 g (10), **or 20-35 g/kg**. The recommended daily salt intake has now been reduced to 2 g daily. So that shows how little cheese is necessary, as part of a healthy diet.

Even if excessive tyramine is ingested and BP increase occurs, serious consequences are most unlikely providing appropriate action is taken. That will usually mean monitoring blood pressure for a 2-3 hours and possibly having medication to lower it (in hospital) if it goes over about 180 – 200 mm Hg *and* there is evidence of harmful

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consequences. Hasty and alarmist treatment of high BP by inexperienced doctors (when there is no evidence of harmful consequences) risks doing more harm than good. Treatment of high BP should generally only be undertaken in hospital (1, 11, 12).

It is quite simple to monitor your own blood pressure with one of the easily available electronic BP monitoring devices that are now on the market. Most people can beg, borrow or buy one of these quite easily. The author always encouraged his patients to obtain one of these devices so that they could keep a record of their blood pressure from the beginning of treatment. The drop in blood pressure caused by these drugs when you stand up is a good indication of whether they are having a sufficient effect. There is a separate PDF on my website explaining blood pressure and MAOIs.

Note: many foods that have elevated concentrations of tyramine also have elevated concentrations of histamine (see below) and other biogenic amines.

**Biogenic amines (BAs) are heat stable:** they are unaffected by all normal cooking processes. Furthermore, decarboxylating enzymes are also heat-tolerant and may survive some cooking operations, allowing continued accumulation of BAs if cooked food is poorly stored.

**Remember that storage of foods below 5°C is a crucial factor,** and some domestic fridges fail the test. It is vital to regularly check your fridge temperature with an accurate thermometer.

## **Introduction**

The drugs in this monograph belong to a group called **Mono-Amine Oxidase Inhibitors (MAOIs)**. The enzyme **Mono-Amine Oxidase (MAO)** has two sub-types, A and B. This information is most relevant for irreversible MAO-A inhibitors (the most common are tranylcypromine & phenelzine) and less important for various other types of MAOI.

This monograph covers diet (both food and drink) and also drug interactions for those on MAOIs. It is intended to inform and assist both doctors, interested non-medical people and those taking MAOIs.

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.

Information such as that contained in here should be given to any person supplying treatment, or advising on any aspect of treatment, including any dentist or medical practitioner. Generally, advice on MAOIs should come from specialist psychopharmacologists. Almost all the information on the Internet is significantly inaccurate, and even the information on sites of educational institutes may be out-dated and misleading. The information provided here is authoritative; the author has published multiple recent papers in prestigious scientific journals on the pharmacology of MAOIs and tricyclic antidepressants (TCAs) and their interactions and has a great deal of first-hand practical experience, see especially references: (1-3, 5, 7, 13-17).

Note: anyone can use Google Scholar, and the National Library of Medicine (PubMed), to find references, mostly with abstracts. If you follow links to journal websites it is surprising how often you can get full-text papers too.

## **The Mechanism of Tyramine Formation**

### **Amino Acids**

Tyrosine is the amino acid precursor for the amine tyramine. Amino acids are the building blocks of proteins. [Wikipedia] "Twenty-two amino acids are encoded by the standard genetic code and are called proteinogenic or standard amino acids; eight are generally regarded

as essential for humans: **phenylalanine**, valine, threonine, tryptophan, isoleucine, methionine, leucine, and lysine. Additionally, cysteine (or sulphur-containing amino acids), **tyrosine** (or aromatic amino acids), histidine and arginine are required by infants and growing children. The amino acids arginine, cysteine, glycine, glutamine, histidine, proline, serine and **tyrosine** are considered conditionally essential, meaning they are not normally required in the diet, but must be supplied exogenously to specific populations that do not synthesize them in adequate amounts.”

Tyramine formation requires the availability of the amino acid precursors tyrosine or phenylalanine 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.

Tyramine’s precursors, but little or no actual tyramine, are present at up to 20 mg/kg in animal protein sources, but are generally lower in plants (see below for exceptions). That is why fresh properly stored foods are always safe. Animal protein can rapidly accumulate tyramine if allowed to go off. That means any meat not stored at proper fridge temperature of less than 4°C. Meats that have been minced are especially prone to bacterial contamination. Poorly handled mince that has been improperly 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. Game birds that have been hung for lengthy periods may be risky, but these will only be encountered in private houses because health regulations do not permit such practices any more in restaurants etc. Some chefs will bend the rules a little but that is unlikely to be sufficient to cause major problems.

Histamine, putrescine, cadaverine, tyramine, tryptamine, 2-phenylethylamine, spermine and spermidine are the most important BAs in foods (18-21); that is why smell is a helpful guide for what to avoid. The smell of putrescine is the key, being the origin of the word putrid. A little of the decaying smell of these biogenic amines is what gives some foods that certain something that gourmets develop a taste for. However, smell is only a guide for what to avoid, tyramine can accumulate without things seeming smelly or ‘off’.

The following list gives an indication of likely tyramine concentrations for relevant substances as indicated by currently available research. It may be used as a guide. It is a lot to do with ‘freshness’ (i.e. time and storage conditions) for fish and meat and

whether tyramine is present depends on the type of micro-organism causing the spoilage.

Older estimations of tyramine concentrations may sometimes be inaccurate because the isolation of amines from complex food matrices is not easy, and usually a derivatisation procedure needs to be applied to enable high pressure liquid chromatography (HPLC) or gas chromatography (GC) determinations.

Again, remember, storage below 4°C is the crucial factor, and some domestic fridges fail the test.

### **What are the Symptoms of a Blood Pressure Reaction?**

A reaction is a slow and progressive increase of BP and usually consists of a thumping heartbeat with an increase in BP. The heart rate (pulse) usually becomes **slower** (22, 23), in response to the increase in BP, not usually, as is sometimes stated, faster. If blood pressure goes up to approximately 180 mm Hg, or more, 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 increase in BP is proportional to the amount of tyramine ingested.** Symptoms usually start soon after eating, usually within 30 minutes. Any symptoms, including headache, starting more than two hours after eating are unlikely to be due to a high blood pressure reaction as the the duration of the reaction is around 1 – 2 hours.

If such a reaction occurs, and nothing is done about it, i.e. getting medical help, then there is a *small* chance that a 'stroke' (cerebral bleed or haemorrhage) would occur, which could be very serious.

## **Tyramine in Foods and Beverages**

Minimising or avoiding the few risky 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 that can make the blood pressure (BP) go *dangerously* high. The seriousness of any BP reaction is in proportion to the amount of tyramine that is consumed. It is a dose-related effect, that is why it is safe to 'test' small quantities of some foods e.g. your favourite local cheese.

It is important to be aware of the components in the food you are eating. Generally speaking, this monograph does not deal with compound foods, e.g. pizza. Such foods can have various types of ingredients that will have widely different tyramine contents. The total tyramine content of such foods will depend on the individual ingredients, but a little common sense and calculation, from the information herein, should yield a reasonable estimate of the likely total amount of tyramine.

**Be aware of the total tyramine load that is contained in a meal, even though individual components may not be particularly high.**

As with everything in life a little knowledge and a little thought are useful.

**MAOIs lower blood pressure.** One of the commonest incorrect statements you will see is that MAOIs raise blood pressure. That is wrong: it is the interaction between tyramine & MAOIs that raises blood pressure, i.e. produces hypertension.

Deaths from tyramine/MAOI induced hypertension are extremely rare, probably rarer than serious reactions to many modern drugs, or to bleeding secondary to SSRIs (24), or being struck by lightning.

**It is neither logical nor reasonable to describe MAOIs as 'dangerous'.**

The opinion has been well argued that the dangerousness idea was much encouraged and spread by, amongst others, pharmaceutical company representatives over-enthusiastically extolling the virtues of newer drugs (25), that necessarily involves exaggerating the disadvantages of previously existing drugs.

Tyramine only accumulates in significant quantities when the amino-acids tyrosine and phenylalanine are converted to tyramine by decarboxylase enzymes possessed by some, but not all, micro-organisms (see e.g. (26)). 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 BAs are monitored as part of food hygiene control audits. Also, special starter cultures that have no decarboxylating micro-organisms in them have been developed. These minimise the proliferation of undesirable bacteria (cf. yoghurt, below) and thereby prevent tyramine formation.

A potentially serious BP reaction can only occur if a relatively large amount of tyramine is eaten or drunk (see list below), i.e. for most people at least 25 mg of tyramine. Most foods with elevated tyramine (like matured cheeses) actually have about 250 mg/kg. Therefore quantities of up to 100 grams of such a cheese are likely to be safe for many people. So, it is obvious that there is no cause for worry if, as an example, a little grated parmesan cheese on a salad has been eaten.

Some of the earliest work on this subject remains instructive. The original papers by Blackwell, e.g. (27, 28), summarise very well some of the basic points that are in this monograph. Seminal early research on the tyramine content of cheeses was done by Kosikowski, e.g. (29). It is interesting to note that of a series of papers he produced in the 1950s none of them has *ever* been cited in the psychiatric literature.

Only very rarely encountered foods have really high tyramine concentrations (such as 1,000 mg/kg, which is exceptionally high) that would require the consumption of at least 25 grams of such a food to get a measurable, but not dangerous, elevation of BP; and that is an extreme example of an exceptionally high tyramine concentration.

## **Milk Products**

### **Mature cheeses**

It is likely that the higher concentrations of 1,000 – 2,000 mg/kg found in older assays will be much less common now. Food regulations have driven widespread use of starter cultures. These contain no bugs with decarboxylase activity which greatly minimises the chance of tyramine production (or other biogenic amines).

Matured ‘artisanal’ cheeses can develop high concentrations of tyramine (~ 1,000 mg/kg), e.g. Stilton, Cheddar, Parmigiano, Manchego, Compté; the older and smellier it is the more tyramine it *probably* contains. ‘Matured’ usually means aged for more than 3 months, rather than just a few weeks (typically 6 months or more). A twenty-five gram serving of such a really strong cheese would have 25 mg of tyramine (i.e. around 1,000 mg/kg), and could possibly raise the BP to a measurable, but not to a dangerous, extent.

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Contrary to what one might think from the paucity of data in the medical literature there have been thousands of tyramine estimations performed from cheeses all over the world: a small selection of studies with extensive and varied sampling is given here to illustrate this.

Most commercial 'supermarket' cheeses are low in tyramine (<100 mg/kg) because budget prices do not pay for long warehouse ageing. Portuguese traditional cheese, Terrincho (30), 29 cheeses from five batches, dairy farms located throughout the region: all < 100 mg/kg. Blue cheese, Czech (31, 32): the mean and median being 380 mg/kg and 289 mg/kg, respectively) and, different cheeses (vats) varied widely, from 10 mg/kg, to 875 mg/kg; and 20 samples of blue cheeses obtained from Spanish retail stores averaged 14 mg/kg, but with a range from 0 to 1585 mg/kg.

Dutch-type semi-hard cheeses mostly < 50 mg/kg, max 250 (33, 34).

Brie and Camembert styles: there seem to be no recent assays, all the author has found is older papers; Horwitz (35, 36) found ~ 100 mg/kg. A little more recently: Camembert, 15 samples 100 – 1800 mg/kg, Brie 260 mg/kg (37, 38). Normally these cheese styles are only matured for 4 weeks before release. One suspects tyramine concentrations are even less now because of starter cultures and better storage.

Compté (5 months old) 1,300 mg/kg.

Lastly, the champion Italian goat cheese at ~ 2,000 mg/kg, very high indeed. It is remotely possible only 5 grams of that would be dangerous. But such specimens are increasingly rare as practices are improving (39).

### Non-matured cheeses

Fresh non-matured, i.e. unripened/unaged, cheese styles, and yoghurt, are always safe because milk itself has no tyramine, e.g. curd styles, *fromage frais*, mascarpone, cream, ricotta, cottage cheeses, *bocconcini*. Tyramine is only present as a result of the action of certain micro-organisms on the proteins in milk. The amount is proportional to the degree of 'contamination' and length of time of ripening: that is why most modern supermarket cheeses have low (< 100 mg/kg) concentrations of tyramine (it costs money to keep cheeses maturing in temperature-controlled warehouses).

Unripened cheeses: 10 samples (40) < 0.5 mg/kg.

Goats cheese (41) '*frais*' styles, usually ~ 20 mg/kg, but aged goats cheeses will be higher, max 70 mg/kg (41).

### Milk and yoghurt

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 (40).

Cho, Korea, Yoghurt, 8 samples, no tyramine to a max of 4 mg/kg (42).

### **Fermented Sauces – Vegetable**

#### Marmite

Marmite is made from residual brewer's yeast and the first production facility was near the Bass beer brewery in Burton on Trent: production started in 1902. It has relatively high amounts of biogenic amines ~ 320 mg/kg of tyramine (43). That is less than Blackwell's original estimate (27) of 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. Vegemite was produced under licence in New Zealand post war, initially to the same formula, but changes were made after various company take-overs.

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

#### Soy sauce, 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 kilo (litre) after many months. Miso is very similar.

Miso, 5 samples tyramine ~ 20 mg/kg (42).

Japanese soy sauce: Maximum 940 mg/L (i.e. approx 1 mg/ml). Most samples measured have ranged between 10-200 mg/L (44). Maximum tyramine concentrations in the past may have been as high as 1000 mg/L (but those may be spurious values), so 25 ml would have contained 25 mg of tyramine.

**Most supermarket Soy sauces actually have ~ 100 mg/L.**

Yongmeia (45), 40 samples of Chinese soy, mostly less than 200 mg/litre (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 **0–673 mg/L for tyramine**, 0–592 mg/L for histamine, 0–550 mg/L for cadaverine, 0–486 mg/L for spermidine and 0–145 mg/L for spermine'.

Stute (46), **23 samples** soy, all low < 200, except one clocked a staggering 6,000 mg/kg (dead rat in the vat one suspects).

Other soy derived products like miso soup and sufu (42, 47) generally have similar concentrations. Miso, 5 samples < 25 mg/kg (42), and soy sauce < 50 mg/kg (42). Sufu Taiwan, histamine 150 mg/kg (48), and Miso 40 samples tyramine all < 10 mg/kg (49).

'Natto' is another fermented soya bean preparation (50).

## **Fermented Sauces: Animal**

### **Fish sauces**

In classical Roman cooking fish sauce was called garum or liquamen. They are ubiquitous now, but 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), ishuru or shottsuru (Japan), colombo-cure (India Pakistan), yeesu (China), aekjeot (Korea). For more see Wikipedia, and for a recent reviews refs (19, 42, 46). 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 its is, like soy sauce, a condiment, so if used in modest amounts (no more than ~ 20 grams) will be safe (51).

Korean fermented fish products < 50 mg/kg (42), liquid fish sauce made from a variety of things, scallop, squid etc average 350, max (anchovy) 600 mg/kg (42).

Stute (46), **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. There seems to be no specific data on tyramine content, but it is reasonable to assume it will be similar to other fish sauces, probably lower. It is usually used in small quantities and is unlikely to add any significant tyramine load to a meal.

## Meat and Fish Products

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 (52), 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 (53). The Hedberg paper is a great illustration of good observation and investigation.

Aged beef can have significant tyramine concentrations, stored at +4°C for 21 days, 60 mg/kg, and after 36 days 120 mg/kg (54). 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).

Ordinary commercial supermarket beef is not usually aged and concentrations are likely to be < 10 mg/kg. Galgano, 7 mg/kg after 8 days at +4°C (55).

Similarly, liver pate (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 (56) has no tyramine, but once processed and contaminated with bugs it would be an ideal culture medium, so any laxity in hygienic preparation practice, storage time and temperature will result in a steady increase in tyramine. Concentrations of 100 – 500 mg/kg are likely in badly stored product after a week or two.

## Meat

### Fresh meats

For a review of amines in meat (and vegetables) see refs (57-59).

Chicken, refrigerated for 20 days at a temperature of +4±1°C in a domestic refrigerator. One day - 3 mg/kg, 20 days - 15 mg/kg (60-62). Moreira found well stored product < 5 mg/kg. Red and white meat refrigerated for 30 days +4±1°C max 30 mg/kg (54).

Beef (63): stored at -18°C for 178 days, tyramine max <4 mg/kg.

Fresh Kidneys (64) and Liver (56), no tyramine.

### Dry cured ham

As with all dry cured meat products only low concentrations of tyramine are expected, Lorenzo found < 5 mg/kg (65), which agrees with (66). So 'Parma ham', prosciutto, copa 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) 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 (26, 67-69).

In their 2003 paper, 'Biogenic amines in dry fermented sausages: a review' Suzzi reviewed 20 studies from all over Europe (70) and found tyramine was usually below 200 mg/kg, very few samples were higher (66). 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 (71).

French sausages, both artisanal and industrial, had tyramine maxima of 270 mg/kg (70, 72).

Things (i.e. hygiene and low temperature processing) are improving steadily, more recent surveys all finding lower concentrations (67, 73, 74).

Latorre-Moratalla et al is a good recent review: it found 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/](http://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. 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 (43). They found none exceeded 10 mg/kg.

## Fish

### Fresh fish

Tyramine and histamine are often both increased, however, with fish spoilage histamine can be greatly elevated without significant

elevation of tyramine. Many regulations limit histamine to between 50 (USA) and 200 mg/kg (EU). Histamine itself causes Scombroidosis (20), see below. **Freshness and handling is everything**, and quality control and screening of imported produce have been a powerful force for improving hygiene world wide. Fresh fish usually has 2 – 5 mg/kg tyramine (75). Whole and filleted trout kept on ice for up to 18 days, max at 18 days was 7 mg/kg (76, 77). Frozen fish 1 mg/kg (78).

Herring, fresh, stored on ice (i.e. ~ 2°C) < 5 mg/kg (79, 80). 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 (75, 81) had a max of 40 mg/kg at end of shelf life.

And, especially re histamine in fish, see (82).

### 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 product may develop significant tyramine concentrations (see below).

### Smoked fish

Smoked salmon (83) dry-salted, traditional smoking, sliced, vacuum-packed stored nine days at 4°C and 19 at 8°C contained no tyramine. Cold smoked salmon < 20 mg/kg (84).

### Dried fish

Dried salted Tuna roe was 90 mg/kg (85).

### Canned fish

Some canned samples reach 10 mg/kg, but that seems rare (86). Max 70 mg/kg (87). Histamine (some were > FDA limit of 50 mg/kg), one was 1,000 mg/kg of histamine! see (88, 89).

### 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 ... well, you can't be helped by this monograph.

### Fish sauces

See 'Fermented Sauces' above.

### Malaysian "budu" and "cincalok"

Malaysian local appetisers "budu" and "cincalok" (51) 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 (90). This is because they are most unlikely to use anything other than commercial processed cheese, or non-matured cheese types (e.g. mozzarella). Also, any salami type products on them are likely to be in small quantities, and also of the type that is low in tyramine. Gourmet pizzas may well 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.

## Vegetables

Vegetables generally have lower amine concentrations, but can these increase with spoilage. And plants do produce an extra-ordinary range of amines and psycho-active alkaloids, many are part of the ancient battle where plants very successfully manipulate the behaviour of animals and to enhance their own survival (e.g. opioids, tannins, nicotine, atropine, hyoscine & innumerable toxins). Many of these compounds are more common in a greater variety of plants

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than a casual reading of the literature would lead one to suppose. Their concentration varies greatly depending on many factors like plant variety, tissue and stage of growth etc.

Useful reviews are: (91, 92).

In summary, it would seem **normal servings** of unprocessed vegetables, fruits etc. are unlikely to have any serious adverse effects via histamine, tyramine or L-DOPA.

Nevertheless, interactions are sometimes noticeable and there is much yet to learn about the psychoactive contents of innumerable 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 seems to contain a constituent that acts as a dopamine re-uptake inhibitor (93).

### L-DOPA

Dopamine (DA) is present in many plants and may play a role in repelling pathogens. It is the precursor of the quinones that cause browning when they polymerise into melanin (e.g. bananas). 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) (94-99). 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* (94), 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. mild 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, and the early papers often quoted, e.g. (100) the evidence for **serious** hypertension (see below for discussion) with L-DOPA and MAOIs seems poor.

Such amounts of L-DOPA may potentiate or precipitate small blood pressure increases, but, in my opinion, it is unlikely that a significant

blood pressure elevation would result unless huge amounts of such foods are ingested, see (101).

### Spinach

Tyramine in spinach (102) was < 5 mg/kg, but histamine can be higher ~ 50 – 100 mg/kg.

### Fava beans

Fava beans (*Vicia Faba*, aka broad beans) have tyramine at about 10 mg/kg (103), & L-DOPA, but at low concentrations, which is probably not sufficient to have any effect in normal portions. See 'L-DOPA'.

### Bananas

Bananas can have significant dopamine, up to 400 mg/kg in the pulp, about 1,500 mg/kg in the skin (104), but little tyramine (105, 106). The first report of dopamine was in 1958 (107). Large amounts of banana (20 per day) may increase plasma dopamine concentrations (101). 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 (108)), 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 (104), at only 2 mg/kg (109) and see (110-112).

Banana may inhibit the adsorption of medicinal L-DOPA (113, 114). It would seem doubtful that bananas in usual quantities would have any significant effect.

### Pickling

Preservation, mostly of vegetables, using the acidic properties of natural acids, mostly acetic & 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 fermentation process, such as 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 Belgian lambic beer) tends to produce more contaminant biogenic amines, including tyramine.

### Sauerkraut

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

Sauerkraut: review (57), **more than 100 samples from 7 countries**, almost all < 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. A spinach sample showed the highest histamine content 20 mg/kg (103).

Korean 'kimchi' cabbage average 50 mg/kg, max 120 mg/kg (42).

From (92, 105) Spinach 2 mg/kg. Histamine concentrations were 100 mg/kg.

### **Miscellaneous**

Any food source that contains protein can theoretically, if allowed to rot, accumulate high tyramine concentrations. Various interesting and strange things are eaten around the world, so a little common sense is needed.

### **Chocolate**

Chocolate sometimes does involve a short fermentation stage. Somewhat variable concentrations of amines have been reported: tyramine concentrations from 9 to 70 mg/kg (115-117).

Pastore (118) found 1 mg/kg for tyramine (10 mg/kg for dopamine, 2 mg/kg for serotonin, 1 mg/kg for histamine, 3 mg/kg for 2-phenylethylamine).

Lavizzari (105) found concentrations of tyramine of: chocolate 0.3, spinach 2, hazelnut 1.8, banana 1, potato 2 mg/kg.

Thus, we can say chocolate is completely safe in usual quantities.

### **Other non-serious, non-dangerous 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,  $\beta$ -phenylethylamine, methylamine, trimethylamine (see Strolin Benedetti & Tipton (119)). 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, agitation, poor sleep etc.

### **Lastly, Some Tyramine Champions**

One soy sauce clocked in at **6,000 mg/kg** (46).

An Italian goat cheese at ~ **2,000 mg/kg** (39)

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 the author was unable to find any data. Would any lab technician 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>

## Wine and Beer

Wine and beer in moderation (two drinks in 2 hours) are definitely safe (as far as tyramine is concerned). Modern hygienic production methods have made excessive tyramine concentrations extremely rare (there is now extensive regulation and documentation of this, see below for details). Badly made drinks may be risky, so take care with 'home-made' wines or beers. Bottled beer is safe; 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 do not 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 (120, 121). One small (330 ml) glass of some 'live' beers could, in *rare* instances, have about 10 mg of tyramine; this might be sufficient to cause a reaction in a minority of people, when taken on an empty stomach, e.g. see (122) and (22).

## Wine

Wine almost never contains significant concentrations of tyramine.

The unquestioning repetition of the notion that Chianti, uniquely amongst wines, contains significant concentrations of tyramine (35), illustrates how easy it is to be careless and unquestioning about the relevance and reliability of sources of information. It has to be said that does not reflect well on the academic standard of many texts, especially since that was contradicted long ago (123). 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 and fermentation techniques. Hygiene practices were poor; it is only in the last 20 years or so that Italian winemaking has reached a modern standard.

Recent major reviews covering many hundreds of different wines of all types: tyramine all < 5 mg/L (124-128).

Aged wines, all < 5 mg/L (129).

Thirty different wines, including aged fortified wines (Port and Madeira), max 5 mg/L (130). Wines 200 samples, histamine average 1.2 mg/L (131) and 300 samples max tyramine < 5 mg/L (132, 133). USA wines, max tyramine 3 mg/L (128).

Marcobal, 61 different Spanish wines including aged Rioja Gran Reserva wines (134). Tyramine range 0–11.32 mg/L, Average 1.40 ± 2.35 mg/L. Only 34 of 61 wines had detectable tyramine.

### Vinegars

Ordinary vinegars low, but: Chinese rice wine (old) 400 mg/L, Sherry vinegar 15 mg/L, Italian Balsamic ~ 15 mg/L (135).

### Beers

Standards, and awareness of brewing hygiene issues, have increased since some of the older results, but some caution is still warranted: it would seem very likely that all standard commercial and modern beers all over the world will be safe, but some low volume ‘artisan’ and ‘boutique’ ones are risky on occasion (see Lambic below).

For a review see (136), although a great majority are low (2 – 8 mg/L) a very few are up to 30 – 50 mg/L.

Tang (137) looked at 18 beers all brewed in China, some European under licence, values mostly 3 – 5 (max 7) mg/L.

Spanish beer < 2 mg/L (138).

17 domestic Turkish and 13 imported beers were evaluated (139) and all were < 2 mg/L.

Ken Shulman’s group (140) looked at a total of **98 beer samples** (79 different brands of beer) 15 years ago, they analysed by HPLC for tyramine: Quote:

*‘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 probably an influential paper, but subsequent results do not quite support all the conclusions.

For instance, some Belgian beers do have high tyramine. Loret et al (141), 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 trying to improve things because of EC regulations and a recommended limit of 10 mg/L.

Older results (1996) from a large number of samples did show some high concentrations, even though averages are low (mostly below 5 mg/L), out of **180 samples** several reached high concentrations.

**Lambic Gueuze was almost 70 mg/L** and there were a few 30s and 50s (142). 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 (141). 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 tranlycypromine. 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 (143-148). The potency of phenelzine for these effects is probably similar, and the blood and tissue concentrations reached in the system are also probably similar. However, there have been no reports involving phenelzine:

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nevertheless one can speculate it is quite possible, indeed likely, that phenelzine will increase people's sensitivity to histamine. Bearing in mind that foods that accumulate tyramine, like cheeses, often have elevated histamine concentrations also, 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). Serum tryptase concentrations may help to distinguish allergic symptoms from scombroidosis (149).

It seems likely, indeed inevitable, that some instances of BA poisoning will exhibit mixed symptoms of both histamine and tyramine effects.

## MAOIs: Interactions with Other Drugs

It is helpful to understand why this text, and review papers, can appear to contradict what is said in authoritative textbooks and other similar sources (e.g. Physicians Desk Reference, British National Formulary, Australian Medicines Handbook). These publications cover a very wide field as concisely as possible and therefore inevitably abbreviate and generalise to an extent that does not allow detailed evaluations. For example, they usually 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. That explains why all tricyclics, except for clomipramine and imipramine, are safe to mix with MAOIs, despite the apparent blanket prohibitions in such texts.

SSRIs interact with other drugs more than do the MAOIs, particularly tranylcypromine (Parnate). Tranylcypromine probably has no clinically significant **pharmacokinetic** interactions (except with CYP450 2A6), but phenelzine, possibly, may have some (1), but still less than SSRIs! The potentially risky interactions are **pharmacodynamic** ones:

1. Serotonin syndrome, caused by SRIs + MAOIs
2. Blood pressure elevation, caused by tyramine in food, or by the other '**indirectly acting sympathomimetic amines (ISAs)**' (releasers) like pseudoephedrine and phenylephrine.

There are less over-the-counter ('OTC', non-doctor scripts) drugs that are a problem now, because pseudoephedrine type drugs (ISAs) have been taken off the market (at least, in some western countries). Pseudoephedrine & related analogues used to be in most cold remedies (nasal decongestants). The commonest non-ISA nasal decongestant is oxymetazoline, which is an adrenergic alpha 2 agonist and is not a problem. Just a little note for drug interaction aficionados: there is a direct parallel between the serotonin mediated toxicity of ecstasy, and its interaction with MAOIs, or SSRIs, that relies on the same mechanism as the noradrenaline mediated hypertensive effect of ISAs. SSRI drugs inhibit the action of ISAs, whereas MAOIs potentiate them. Similarly, NRIs block the effects of tyramine, and other ISAs, whereas MAOIs potentiate them. Directly acting agonists, including adrenaline itself, are not a problem with MAOIs. It is only the indirectly acting adrenaline-like drugs (i.e. ISAs like pseudoephedrine), whose action is to release adrenaline from the presynaptic nerve, that are a risk.

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MAOI interactions are clearly understood and are straightforward to avoid. There is not room for a lengthy discussion on this subject here, but readers may note that the author has published widely concerning both pharmaco-kinetic and pharmaco-dynamic interactions, and cytochrome P-450 characteristics, of most psychotropic drugs. These papers should be consulted by those wishing to have more understanding of this complex subject. These provide the back-ground knowledge for understanding these interactions which will be helpful for those unsure of the latest data (bearing in mind that standard texts may contain insufficient detail and therefore be misleading). See especially the reviews- (1-5, 7, 14, 16, 17, 150, 151).

The anti-histamines brompheniramine and chlorpheniramine are best avoided because they have weak, but possibly significant, SRI potency. All other anti-histamines are safe (152).

Analgesics (pain killers) that are **safe** to take with MAOIs:- Aspirin and Paracetamol and all the 'NSAIDs' (anti-inflammatory drugs used for arthritis), such as: ibuprofen, mefenamic acid, naproxen, indomethacin, phenylbutazone etc. and the newer 'COX2' drugs.

All anti-anxiety drugs (benzodiazepines) like diazepam, oxazepam and temazepam are safe.

Stronger analgesics (narcotics or opioids, like morphine)

- Safe: codeine, oxycodone, buprenorphine and morphine.

### **Risky Analgesics**

The risk with opioid (narcotic) analgesics is that of serotonin toxicity (ST) or 'serotonin syndrome', which is quite different to the hypertensive reaction with tyramine (153). This is explained in detail in this author's review (17), which is the only recent comprehensive review on this topic. Some analgesics are risky because they are serotonin reuptake inhibitors. Pethidine (aka meperidine) and tramadol, especially, are a significant risk for anyone on MAOIs. Dextromethorphan, (dextro)propoxyphene and pentazocine are also best avoided.

### **Anti-Depressant Drugs**

Any drug that works as a serotonin reuptake inhibitor (SRI) is potentially dangerous (possibly even fatal) if combined with an MAOI, including reversible inhibitors of monoamine oxidase A (RIMAs) like moclobemide (2, 150). If people have been taking any serotonin reuptake inhibitor type drug including:-- **sertraline, fluoxetine, paroxetine, fluvoxamine, citalopram, escitalopram, clomipramine or imipramine, or SNRIs like milnacipran, venlafaxine, desvenlafaxine, duloxetine or sibutramine** recently

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then specialist advice may be needed before starting any MAOI or a RIMA like moclobemide.

NB 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, dothiepin, desipramine, doxepin are quite safe (as are selective NRIs like reboxetine and atomoxetine).

On ceasing other antidepressants to start MAOIs, washout intervals varying between one and five weeks may be required (the rule of thumb is allow 5 half-lives to elapse, which is about one week for many of these drugs). No washout is required for TCAs (other than clomipramine and imipramine), or mirtazapine, mianserin, trazodone or reboxetine, because they are safe taken together with MAOIs.

### Fluoxetine

If the SSRI fluoxetine has been taken (Prozac and other names) within the previous two months caution is required and specialist advice may be needed before starting various drugs, but particularly any MAOIs including moclobemide. This is because fluoxetine (via its metabolite nor fluoxetine) has an elimination half-life in some people of up to two weeks (so it can take 6-10 weeks to get out of the system).

### Anti-Psychotic drugs

All available anti-psychotic drugs have, until recently been safe with MAOIs. However, one newer so-called atypical one, ziprasidone (Zeldox), seems to possess serotonin reuptake inhibitor potency. There has been a typical case of moderately severe serotonin toxicity reported with it in combination with tranylcypromine (154). This is a strong signal that its serotonin reuptake inhibitor in potency can be significant and can cause severe serotonin toxicity if mixed with MAOIs. Therefore this combination should be avoided until further information is available, or used with *extreme* caution.

### Triptans

Because the FDA have issued a warning about triptans and serotonin toxicity it is appropriate to draw attention here to this author's review of this subject (4), published a little while ago in the journal Headache. Not only did the FDA issue a warning about potentially *fatal* toxicity, but the usually reliable journal the 'New England Journal of Medicine' also published a poorly argued letter (155) promoting the same idea (and declined to publish, a rebuttal of it). It is concerning that such scientifically dubious and low value case report material still gets published at all, never mind in the

NEJM. It appears clear that this warning is misconceived and that there is no evidence for a risk of serious serotonin toxicity from mixing triptans with either SSRIs or MAOIs. For those who are interested full details can be read in the review paper. Lastly, 20 months down the track, there has been no published rebuttal of anything in that review, neither by the FDA nor by anyone else. Several other reviews and comments support the author's position (156-158).

### **Ceasing Treatment**

This advice on diet and possible interacting drugs should be followed for a minimum of two weeks (six weeks in some situations) after ceasing MAOIs (between one and three days in the case of moclobemide).

## **Medical Treatment of High BP Resulting from Tyramine Ingestion**

If excessive tyramine is ingested in cheese etc. blood pressure starts to increase from about half an hour after ingestion, and remains elevated for 1 – 2 hours. Current evidence suggests that elevated BP without signs or symptoms of ‘end organ’ damage does not require treatment, *and should not be treated*. This is because rapid BP reduction may do more harm than the short term BP elevation (usually less than 2 hours) caused by tyramine. Rapid control (i.e. within 1-2 hours) of hypertension that does not also exhibit definite end organ damage does sometimes result in serious adverse effects (12, 159, 160). Generally, treatment should only be initiated when there is definite evidence of *acute and rapidly evolving end organ damage*. Several recent reviews make strong statements about premature treatment in the absence of end organ damage: e.g. 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*”.

**It is generally inadvisable for treatment to be initiated by psychiatrists:** on the rare occasions where treatment is required it is best initiated after admission to a critical care setting (1).

It is noteworthy that pain and anxiety both exacerbate hypertension, so remaining calm and using a benzodiazepine (which usually lowers BP to a significant extent (161)), whilst instituting measures to assess any possible developing end organ damage, is probably the most important step. The most appropriate hypotensive agent will depend on the particular end organ affected (brain, heart, lungs, kidneys). Note: sub-lingual nifedipine is now generally considered contraindicated because it has an unpredictable effect: it should not be given to patients to self-administer (11, 160).

**These observations exemplify why psychiatrists are strongly advised to refer such cases (see Transfer Of Care protocols) and not to attempt management themselves.**

## **Transfer of Care Protocols**

It would seem advisable for any specialist, or hospital psychiatric unit, that utilises MAOIs to have a formal transfer of care (TOC) protocol in place for the management of uncommon incidents where patients develop significant hypertension. Indeed, it is part of the treating doctors’ duty of care to make sure such protocols are in place and functioning. In the rare instances where emergencies arise

coordination of monitoring, care and *possible* treatment with the receiving hospital is extremely important. There are too many stories of patients being sent to the local emergency department where they have sat for an hour, or more, before being seen, sometimes by doctors who do not even know what MAOIs are, never mind what to do, or not to do, for a patient who has some degree of hypertension (162). That kind of eventuality is unacceptable and leads to successful negligence actions against the doctors and hospitals concerned.

See Jorm (163), et seq. and website of “The Australian commission on safety and quality in health care”

<http://www.safetyandquality.gov.au/internet/safety/publishing.nsf/Content/home>

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