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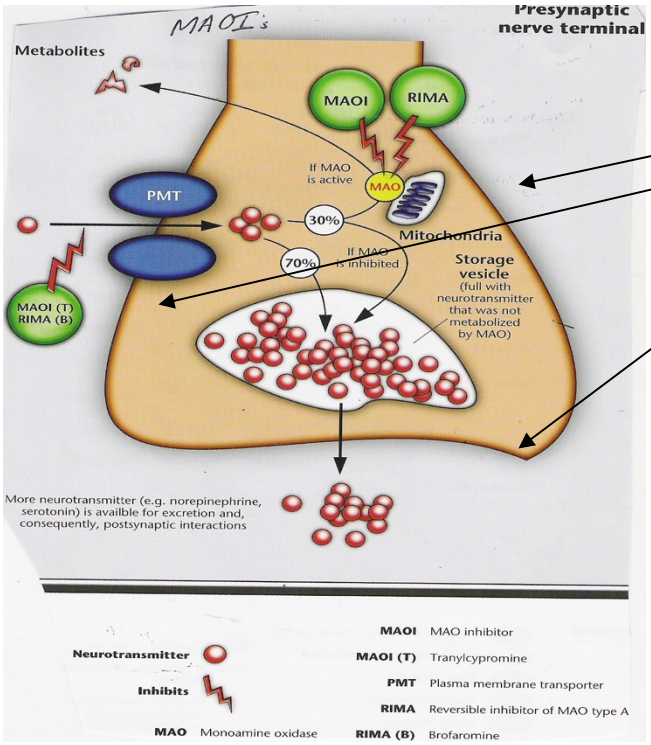
Anxiety and Depression Treatments: Monoamine Oxidase Inhibitors (MAOIs)

- **General**
  - Introduced in the 1950's
  - Adult evidence of safety and efficacy; inadequate evidence of safety and efficacy in children
  - MAO-A:
    - metabolizes serotonin, norepinephrine, dopamine, and tyramine
    - present in brain, gut, liver, placenta, and skin
  - MAO-B:
    - metabolizes dopamine, phenylethylalanine, histamine, (and less so tyramine)
    - present in brain, platelets, lymphocytes
  - Tyramine potently releases norephinephrine (which is relevant to the risks detailed below)
  - Non-selective MAOI's have greater effects on inhibiting MAO-A than MAO-B
  - Ratio of MAO-A to B
    - Brain: 25% to 75%
    - Liver: 50% to 50%
    - Gut: 80% to 20%
    - Nerves: 90% to 10%
  - The non-selective irreversible MAOI's covalently binds to MAO-A and B and permanently deactivates the enzymes; enzyme activity cannot be restored until the body replaces the enzyme through new enzyme synthesis, which can take up to two weeks
  - Monoamine oxidase (MAO) concentrations or activity is increased in the prefrontal cortex and anterior cingulate cortex in 34% of depression studies; victims of suicide also show elevations in MAO
  - See also the bottom of the packet for info developed from a colleague
  - Genetics/biology
    - The T941G mutation (which has a G allele), when its inherited from both parents, creates a more robust MAO-A enzyme that is 75% more efficient at monoamine degradation and is often more often associated with major depression than its less active T allele variation.
    - There is also a variable tandem repeat mutation (MAOA-uVNTR) where the long allele is associated with
      - a greater risk to develop major depression
      - worse outcomes in patients with major depression and histories of childhood trauma
      - greater suicide risks in males with major depression
      - loss of top-down control from the ventromedial prefrontal cortex to the amygdala with resultant hyperactivity in the amygdala, which is associated with
        - loss of harm avoidance
        - more impulsivity
        - loss of prosocial reward-seeking
    - Too much MAO activity, with resultant depletion of serotonin, norepinephrine, and dopamine, may lead to
      - reduced neuroprotrection
      - increase toxic chemicals
      - decreased mitochondrial ATP production
      - altered cerebral energy metabolism
      - abnormal increases in cell death/damage and brain atrophy
    - R1
      - Upstream transcription factor protein whose function is to lower the production of MAO-A
      - R1 is deficient (and MAO-A less reduced) in patients with major depression and victims of suicide
    - Gender
      - Estrogen inhibits MAO activity (so that when estrogen levels decrease in women quickly after delivery. MAO activity increases
      - The MAO gene is located on the X-chromosome
      - In males, the SRY protein, coded on the sex-determining region of the Y sex chromosome, regulates the expression of the MAO gene on the X-chromosome; SRY, along with steroidogenic factor 1 (SF1), inhibit MAO activity
      - Females have two copies of the X-chromosome, one of which is inactivated. Sometimes incomplete X inactivation leads to an excess of MAO-A expression and activity
  - First MAOI was iproniazid, used in the treatment of tuberculosis, called a "psychic energizer" by Nathan Kline in 1957



Adderall/Dexedrine to a minimal extent

- Efficacy
  - Quitkin, et al: phenelzine superior to amitriptyline for atypical depression (> 400 patients)
  - Henkel, et al: similar though less dramatic superiority over TCA's
  - STAR-D study: tranylcypromine not superior to combo of Effexor XR and Remeron
  - Outpatients:
    - Average: 50-70% response rate
    - Atypical depression:
      - Early onset, chronic: 71-80% response rate (more than TCA's)
      - Late onset, non-chronic: 71-80% response rate (same as TCA's)
    - Elderly, severe depression: More relapse prevention than TCA's
    - Treatment-resistant depression, typical: 33% response rate
    - Panic disorder
    - Social anxiety disorder: 60-70% response rate
      - Liebowitz et al, 1999
      - Heimberg et al, 1998
      - Versiani et al, 1992
      - Liebowitz et al, 1992
      - Gelernter et al, 1991
    - Bipolar depression
  - Inpatients
    - Average: ?Less effective than TCA's
    - Severely depressed inpatients: Comparable to ECT and TCA's
  - More efficacious when co-morbid panic
- Side effects:
  - Lack of orgasm, sexual dysfunction
    - 22% Nardil
    - 2% Parnate
    - can use cyproheptadine 1-4 mg/pm or bethanechol 10mg 30 min before sex for erectile dysfunction; avoid stimulants, Remeron, Buspar, Wellbutrin as antidotes.
  - Dizziness/fainting
    - 11% Nardil,
    - 17% Parnate
    - due to low blood pressure on standing
    - must maintain hydration, increase salt, use support stockings
    - can add fludrocortisone 0.6-0.8 mg/day.
    - an expert psychopharmacologist could very carefully add a low dose of a stimulant, though runs risk of hypertensive crisis
  - Hypomania

        - 10% Nardil,
        - 7% Parnate
    - Weight gain
        - 8% Nardil
    - Urinary hesitancy
        - 5% Nardil
        - 2 % Parnate
    - Disorientation
        - 5% Nardil
        - 2% Parnate
    - Paresthesia
        - 5% Nardil
        - 2% Parnate; use pyridoxine
    - Swelling
        - 4% Nardil
        - 0% Parnate
        - consider hydrochlorothiazide up to 50 mg/day or amiloride 5-10 mg/day.
    - High body temperature
    - Insomnia with daytime sedation
    - Muscle cramps
    - Constipation (less than with TCA's)
    - Dry mouth (less than with TCA's)
    - Myoclonic twitches; muscle pain; painful sensations/tinglings—pyroxidine 100 mg/day may help.
    - Activation in day (more with Parnate)
    - If dose too high: balance problems, confused, euphoric
    - Serotonin syndrome
        - Precipitated by concomitant administration of opioids or SSRI's
        - At least 3 of:
            - changes in mental status
            - agitation
            - myoclonus
            - hyperreflexia
            - fever
            - shivering
            - sweating
            - incoordination
            - diarrhea
    - High blood pressure crisis (when in combo with certain foods/drinks/sauces/meds)
        - 8% Nardil
        - 2% Parnate
        - General
            - in the past before dietary restrictions were used, the rate was 2.4-25% of which up to 25% experienced stroke or death
            - in the past (e.g., early 1960's), when the tyramine content in foods was much higher and there were no dietary guidelines, only 14 deaths were reported among an estimated 1.5 million patients who took MAOI's
            - MAOI's do not by themselves raise blood pressure (in fact, they can cause orthostasis)
            - Routine exercise or other vigorous activities (like weight lifting) can raise systolic blood pressure well above 200 mm Hg, and routine baseline systolic pressures, ranging from 180-220, do not increase the risk of stroke
            - when combined with certain foods, medications, and alcohols)
            - carry a Med-Alert card
            - hospital evaluation is needed only if a substantial amount of tyramine is ingested (e.g., ~100 mg or more) and self-monitoring shows a systolic blood pressure of >220 mm Hg over a prolonged period (e.g., 2 hours); see below for examples of tyramine content of common foods
            - all folks on MAOI's should purchase a portable blood pressure cuff for times when one experiences a headache within 1-2 hours after tyramine ingestion
            - most reactions are self-limited and resolve over 2-4 hours
            - folks who ingest 100 mg or more tyramine should be evaluated by a physician
        - Symptoms include:

- severe occipital/temporal headaches
- sweating
- pupil dilation
- increased blood pressure
- palpitations
- neck stiffness
- muscle twitches

- ***Foods, medications, alcohols to avoid***:
  - Vegetables/fruit
    - Fava
    - Broad bean pods, Italian green beans
    - Banana peel
    - ***Acceptable foods:***
      - All other vegetables
      - Banana pulp (other than peel)
      - All other fruits
  - Meat, poultry, and fish
    - Air dried, aged and fermented meats, sausages and salamis
      - Dry/hard sausage, from Europe (primarily)
        - Up to 200 mg tyramine per kg or L (rare: up to 600 mg)
        - 125 g (4.4 oz) → 25 mg tyramine (rare, if 600 mg: 42 g (1.5 oz)
      - Cacciatore
      - Mortadella
    - Smoked fish (e.g., pickled herring), at least if it is improperly stored
    - Liver (beef or chicken)
    - Any spoiled or improperly stored meat, poultry and fish, animal livers
    - ***Acceptable foods:***
      - Fresh meat, poultry and fish
      - Beef/chicken bouillon
      - Fresh processed meats
        - Lunch meats
        - Hot dogs
        - Breakfast sausage
        - Cooked sliced ham
  - Dairy
    - *Matured, aged, artisanal cheeses
      - Up to 1000 mg tyramine per kg or L
      - 25 g (0.88 oz) → 25 mg tyramine
    - Aged feta
      - Up to 250 mg tyramine per kg or L
      - 100 g (3.5 oz) → 25 mg tyramine
    - Commercial cheeses and cheddar/grana Padano/pecorino/provolone/ripened goat cheese/emmental/taleggio/bel paese
      - Up to 200 mg tyramine per kg or L
      - 125 g (4.4 oz) → 25 mg tyramine
    - Parmigiano reggiano
      - Up to 150 mg tyramine per kg or L
      - 167 g (5.9 oz) → 25 mg tyramine
    - Edam
      - Up to 120 mg tyramine per kg or L
      - 208 g (7.3 oz) → 25 mg tyramine
    - Gouda, gruyere
      - Up to 100 mg tyramine per kg or L
      - 250 g (8.8 oz) → 25 mg tyramine
    - Casseroles made with these cheeses (e.g., lasagna)
    - ***Acceptable foods:***
      - Processed cheeses
      - Mozzarella
      - Ricotta cheese
      - Cottage cheese
      - Cream cheese
      - Yogurt
      - Sour cream

- Ice cream
- Must be fresh and stored properly

- Drinks
  - ALL tap beer, other beers that have not been pasteurized
  - Red wine
  - ***Acceptable foods:***
    - Use of alcohol not recommended
    - No more than TWO bottled or canned beers OR TWO 4 fl. oz glasses of red or white wine per day
    - This applies to NON-alcoholic beer also
    - Red wine might produce headache unrelated to a rise in blood pressure
- Other
  - Concentrated yeast extract, such as Marmite/Vegemite
    - Up to 300 mg tyramine per kg or L
    - 75 g (2.64 oz) → 25 mg tyramine
  - Sauerkraut
    - Up to 200 mg tyramine per kg or L (rare reports of up to 900)
    - 125 g (4.4 oz) → 25 mg tyramine (rare (if total is 900): 28 g (0.98 oz))
  - Kimchi
    - Up to 120 mg tyramine per kg or L
    - 208 g (7.33 oz) → 25 mg tyramine
  - Specialty soy sauce
    - Up to 940 mg tyramine per kg or L
    - 27 g (0.94 oz) → 25 mg tyramine
  - Commercial soy sauce
    - Up to 200 mg tyramine per kg or L
    - 125 g (4.4 oz) → 25 mg tyramine
  - Fish sauce (e.g., Nam-pla, etc)
    - Up to 500 mg tyramine per kg or L
    - 50 g (1.8 oz) → 25 mg tyramine
  - Most soybean products, including soy sauce, sherry, tofu (especially fermented tofu), tempeh, tamari sauce, miso soup
  - ***Acceptable foods:***
    - Brewer's yeast
    - Baker's yeast
    - Soy milk
    - Commercial chain restaurant pizzas prepared with cheeses low in tyramine (and NOT with aged cheeses)
- If taken in large amounts
  - alcohol
  - ripe avocado
  - yogurt
  - bananas (ripe)
  - chocolate
  - figs
  - meat tenderizers
  - caffeine-containing beverages
  - raisins
- Meds (also may cause serotonin syndrome)
  - Meperidine (Demerol)
  - Epinephrine
  - Anesthesia
  - Cocaine
  - Weight loss products
  - Local anesthetics (containing sympathomimetics)
  - Decongestants (over-the-counter or prescribed)
  - Dextromethorphan
  - Over-the-counter supplements containing tyramine
- Patients should carry a card summarizing what foods should be avoided
- Use 1 pharmacy and run ALL medicines by prescribing psychiatrist

- **Include:**
  - **Irreversible inhibitors of MAO-A and MAO-B**
    - **Marplan**—isocarboxazid
      - FDA-approved for depression in 1959
      - Start at 10 mg/pm

        - 30-60 mg/day
        - 10 mg tabs
        - Side effects
            - sexual dysfunction
            - weight gain
            - orthostatis
            - hypertensive events (if don't follow "MAOI diet")
            - serotonin syndrome (if mix serotonergic meds with it)
    - **Nardil**—phenelzine
        - FDA-approved for depression in 1961
        - start at 1 mg/kg/day (often 15 mg/day) at night
        - 45-75 mg/day (max 90 mg/d); twice-daily dosing
        - 15 mg tab
        - half-life is 2 hours (which is only relevant for side effects)
        - Relative to other MAOI's:
            - more sedating
            - can cause insomnia
            - orthostatic hypotension
        - Other side effects
            - weight gain
            - sexual dysfuntion
    - **Parnate**—tranylcypromine
        - FDA-approved for depression in 1961
        - Start at 0.7 mg/kg/day (often 10 mg/day) at night
        - 30 mg/d (max 60 mg/d)
        - 10 mg tabs
        - Half-life is 0.75-1.5 hours (depending on the enantiomer), which is only relevant for side effects
        - Side effects
            - more stimulating at higher doses
            - can be activating in the day and cause insomnia at night (structurally related to amphetamine)
            - sexual dysfunction
            - weight gain
            - orthostasis
            - hypertensive events (if don't follow "MAOI diet")
            - serotonin syndrome (if mix serotonergic meds with it)
    - **Clorgyline**
        - selective, irreversible MAO-A inhibitor
        - some evidence of efficacy in pediatric ADHD
        - not available
    - **Selegiline** (oral)
        - See below for transdermal selegiline (Emsam)
        - FDA-approved for Parkinson's disease in 1991.
        - an MAOI at doses greater than 20 mg/day
        - short half-life, requiring multiple daily dosing
        - May be effective in depression and pediatric ADHD.
        - Neuroprotective properties
            - Increases brain-derived neurotrophic factor and glial cell-derived neurotrophic factor
            - Less so than rasagiline (below)
        - Metabolites include l-amphetamine and l-methamphetamine, both of which are dopamine and norepinephrine reuptake inhibitors.
        - Oral disintegrating formulation developed for Parkinson's disease: 1.25-2.5 mg/day
        - At 5-10 mg/day, selective irreversible MAO-B inhibitor, increasing dopamine; at this dose range (or up to 2.5 mg/day if administered in the oral disintegrating ZYDIS form, there is no tyramine hypertensive response
        - At 20-60 mg/day, which is required for efficacy in depression, both MAO-A and B inhibitor
        - side effects
            - stimulating at higher doses
            - nausea
            - dizziness
            - orthostasis/falls
            - abdominal pain
- **Reversible inhibitors of monoamine oxidase A (RIMA)**
    - Moclobemide **(Manerix/Aurorix/Arima)**
        - Several thousand patients with depression studied over last 10 years; found to be effective depressive illnesses and bipolar subtypes; as effective as amitriptyline, imipramine, clomipramine, and fluvoxamine
        - Found t be effective in social phobia
        - Not available in the U.S. for commercial reasons; available in Europe, Canada, and other parts of the world
        - Half-life 1-3 hours
        - 300-600 mg/day, given after meals or at bedtime (to minimize dietary interactions).

- Most common side effect nausea, but also:
    - Insomnia
    - Dizziness
    - Agitation/anxiety
    - Restlessness
    - Dry mouth
    - Diarrhea
    - Constipation
    - Galactorrhea
    - Rare hypertension
- Low risk of dietary interactions; in Europe, the only restriction is avoiding large amounts of aged cheeses after taking a dose of the drug.
- Take after meals

- **Befloxatone**
    - Not available in the U.S.
    - Also blocks serotonin reuptake; 20% the potency of Prozac
- **Brofaramine**—not available in the US
- **RS-8359**—under development
- **Cimoxatone**—under development
- **Roloxatone**—under development
- Linezolid (Zyvox)--antibiotic
- Methylene blue--treats cyanide poisoning and other conditions

- **Other**
    - **Selegiline/Emsam** (transdermal selegiline)
        - FDA-approved for depression as of 3/06; no dietary restrictions with the lowest-dose version of the patch—6 mg/24 hours
        - Evidence
            - Effective in treating depression in at least two studies
                - DelBello, 2014, Adolescent depression, 308 adolescents, flexible dosing, vs. placebo
                    1. Not more effective on the whole
                - Feiger et al, 2006, one of the studies
                    1. Adults, 8 wk, DB RCT, 6-12 mg/24 hours
                    2. safe and effective
                    3. insomnia and application site rash biggest side effect
                    4. no hypertensive crises.
            - Social phobia
                1. 2013: 12-week, open-label, pilot study in 20 patients
                2. Effective
                3. Side effects
                    1. Headache 25%
                    2. Application site reactions 20%
            - Pediatric depression
                - DelBello et al, 2011; 308 adolescents with major depression
                    1. Emsam with 58.6% response rate vs. placebo with 59.3% response rate (note: that is an extraordinarily high placebo response rate
        - May be more potent MAO-A inhibitor in the brain than Eldepryl
        - Bypasses gut and liver, allowing for higher plasma levels with a lower risk of foodstuff interactions and serotonin syndrome
        - Half-life 20.1 hours
        - Will be available in 6, 9, 12, 20, 30, and 40 mg/24 hours applied daily
        - Starting dose ~20 mg; daily dose increased by 10 mg every 1-2 weeks to maximum 40 mg.
        - Hypertensive reaction still possible, but much more unlikely; none seen in initial trials at 6 mg/24 hours dose
            - First symptom is headache
        - Insomnia can be problematic
        - Wait three weeks before stopping an older MAOI and starting selegiline.
        - Wait 7-10 days after cessation of selegiline before beginning a serotonergic medication.
        - Do not need to follow MAOI diet if the lowest patch (6 mg/24 hours) used
        - Do need to avoid:
            - Many cough and cold preparations
                - Pseudoephedrine—no clinically significant changes in blood pressure seen
                - Phenylpropanolamine—higher incidence of blood pressure elevations but no longer commercially available in the US.

- Nasal decongestants
- Hay-fever medications
- Sinus medications
- Asthma inhalant medications
- Anti-appetite medications
- Weight-reducing preparations
- "Pep" pills
- General anesthetics
- Cocaine
- Herbal or dietary supplements containing tyramine
- Cyclobenzaprine
- Due to risk of serotonin syndrome
  - Most other antidepressants
  - St. John's wort
  - Other MAOI's, including selegiline
  - Certain analgesics (e.g., Demerol)
  - Dextromethorphan
  - Buspirone
  - Carbamazepine (Tegretol)
  - Oxcarbazepine (Trileptal)
- Do not stop abruptly; abrupt cessation can cause nausea, dizziness, and hallucinations
- Does not seem to cause orthostatic hypotension or sexual dysfunction; may cause less insomnia.

- Specific side effects

***Insomnia (9 or 12 mg/24 hr patch)**	**32% vs. 7% placebo** **10-12% with 6 mg/24 hour patch**
***Rash at skin patch site**	**24% vs. 12% placebo**
Headache	16-21% vs. 17% placebo
***Dizziness (9 or 12 mg/24 hr patch)**	**14% vs. 5% placebo** **4% with 6 mg/24 hr patch**
***Anxiety/nervousness (9 or 12 mg/24 hr patch)**	**15% vs. 7% placebo** **5% with 6 mg/24 hr patch**
***Orthostatic hypotension**	**9.8% vs. 6.7% placebo**
Diarrhea	8-11% vs. 7% placebo
Dry mouth	7-13% vs. 6% placebo
***Discontinuation due to side effects**	**7.1% vs. 3.6% placebo**
Nausea	4-7% vs. 6% placebo
***Rash**	**4% vs. 2% placebo**
Somnolence	3-5% vs. 3% placebo
Weight gain of 5% or more of total weight	2.1% vs. **2.4% placebo**
Abnormal dreams	2-5% vs. 2% placebo
***Weight loss**	**5% vs. 2.8% placebo**
Average of 2.64 weight loss with Emsam	
Average of 0.66 weight gain from placebo	

- Sexual side effects (these may be underestimates due to underreporting)

Abnormal ejaculation	1% vs. 0% placebo
Decreased interest	
males	0.7% vs. 0% placebo
females	0% vs. 0.2% placebo
Erectile dysfunction	0.7% vs. 0.4% placebo
Lack of orgasm	
males	0.2% vs. 0% placebo
females	0% vs. 0% females

- **Pargyline**—not available in U.S.; MAO-B inhibitor; mixed evidence of efficacy in pediatric ADHD.
- **Rasagiline**
  - selective, irreversible MAO-B inhibitor
  - 10-15 times more potent than selegiline
  - Metabolite is aminoindan
  - does not give rise to methamphetamine metabolites
  - does not have the sympathomimetic activity of selegiline; is not vasoactive
  - Once daily administration is efficacious and well-tolerated as initial monotherapy in patients with early Parkinson disease and as an adjunct in levodopa-treated patients with Parkinson's
  - Robust neuroprotective activity; slows progression of early Parkinson's
    - Increases brain-derived neurotrophic factor and glial cell-derived neurotrophic factor
  - At 1 mg/day, does not induce hypertensive response to tyramine
- EVT 302
  - MAO-B inhibitor
  - Being studied for use in Alzheimer's

- **Management of MAOI's**

- Must have a 2-week washout period after all SSRI's except Prozac (which requires 5 weeks) and 1 week after Effexor before starting MAOI's.
- Must have a 2-week washout period after MAOI's prior to starting an SSRI or an SNRI.
- Wait three weeks before stopping an older MAOI and starting selegiline.
- In very severe, treatment resistant depression, an expert psychopharmacologist can very carefully combine
    - MAOI's and tricyclic antidepressants
        - best to start them at the same time
        - adding TCA to the MAOI is MORE DANGEROUS than vice versa
        - NEVER clomipramine
        - BEST TCA to add:
            - amitriptyline
            - trimipramine
        - BEST MAOI to have TCA added:
            - phenelzine
            - isocarboxazid
    - add stimulants to MAOI's to combat sedation or low blood pressure (with careful blood pressure/heart rate monitoring).
    - add trazodone to MAOI's for insomnia
    - add atypical antipsychotic (except for Geodon, which has SNRI properties)
    - add lithium (though some risk of serotonin syndrome)
    - add thyroid hormone
    - ?add Mirapex
    - ?Lamictal (though some risk of serotonin syndrome)

From a colleague:

- General
    - Monoamine oxidase inhibitors (MAOIs) were the first class of antidepressants in clinical use. They were discovered in 1952 after iproniazid (a derivative of the antibiotic isoniazid) was found to be a potent antidepressant. Soon thereafter, tranylcypromine and phenelzine were developed as MAOI antidepressants. What these medications have in common is the property of irreversibly blocking monoamine oxidase, the enzyme responsible for the oxidative deamination of neurotransmitters such as serotonin, norepinephrine, and dopamine. This property is thought to be largely responsible for the MAOIs' antidepressant effects.

    - MAO is distributed in tissues throughout the body. The blockade of MAO in the gastrointestinal tract is responsible for the "cheese reaction" associated with MAOIs. This refers to a severe hypertensive crisis that can occur after patients on MAOIs ingest foods containing the sympathomimetic tyramine. Tyramine is usually metabolized in the gastrointestinal tract, but the blockade of MAO allows it to flow into the general circulation.

    - MAOIs have potent hypotensive effects, and thus may cause dizziness (from low blood pressure, especially in the elderly). Other common side effects are insomnia, dry mouth, gastrointestinal upset, and urinary hesitancy.

    - People who are on these drugs should keep some means of identifying the fact that they are on MAOIs readily available, in case of accidents or emergencies. This may be: medical alert bracelet, and/or information readily available on phone or in handbag/purse/wallet. Most important: Avoid medications that affect serotonin and norepinephrine. In particular this means avoiding all the SSRI and SNRI-type antidepressants; the synthetic opioids meperidine (Demerol) and pentazocine (Talwin); the cough suppressant dextromethorphan; and all cold medications, especially those containing pseudoephedrine (unless you call me to discuss a specific one).

    - The main foods to avoid are aged cheeses, aged meats, and soy sauce.

- MAOI restrictions

    - 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 favorable conditions for their growth and decarboxylating activity exist then tyramine (and other biogenic amines) may accumulate in foods. Fresh properly cold-stored

foods are always safe. Animal protein will accumulate tyramine if allowed to go 'off'. Meat and fish must be stored at a refrigerator temperature of less than 5°C. [Ground meat is especially prone to bacterial contamination: poorly handled ground meat that has been improperly refrigerated could accumulate significant tyramine quickly].

- The symptoms of a hypertensive reaction

    - A hypertensive reaction is a progressive increase in 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 in response to the increase in BP. If systolic blood pressure (SBP) goes above around 180 mm Hg, rapid onset of severe headache is usual. Tightness in the chest and paleness (pallor) may occur.

    - The degree of increase in BP is proportional to the amount of tyramine ingested. BP elevation starts soon after ingestion (generally within an hour) and symptoms may occur soon after. Any symptoms, including headache, that begin 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 one or two 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 referred to as a 'hypertensive urgency'. In hypertensive urgencies the treatment aim is to reduce BP slowly. Since tyramine reactions are self-limiting over about two hours, even moderately severe reactions will very rarely require intervention. 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.

    - If you think you are having a hypertensive urgency or emergency (for example, you ate something like cheese, and soon thereafter developed a severe headache), sit down, check your blood pressure as calmly as you can, and call me on my emergency line: (917) 573-9600. If I am not available (which is rare), leave me a message and then call my covering doctor (Dr Pelton), or the emergency room. Based on your blood pressure and symptoms, we may need to send you to the emergency room, but that is unlikely. If available, dissolve Ativan (lorazepam) 1mg under your tongue right away, and try to keep calm.

- Tyramine in foods and beverages

    - Tyramine concentrations for ordinary foods depend on storage time and storage conditions. Modern food hygiene and handling practices and regulations mean that excess tyramine levels are unheard of in 'fresh' foods. That leaves those foods that are deliberately produced using

microorganisms. Minimizing or avoiding the very few high tyramine foods and beverages that do exist is easy and necessary. 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. It is therefore permissible and safe to cautiously 'test' small quantities of some foods e.g. your favorite cheese.

- 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 minimize the formation of undesirable 'off' flavors. They also minimize the proliferation of undesirable contaminant organisms and thereby greatly lessen, or even prevent, tyramine formation. Further, modern food hygiene practice involves monitoring biogenic amines as part of food quality and hygiene audits.

- 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 individuals, 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.

- Specific foods

  - https://psychotropical.info/wp-content/uploads/2018/02/MAOI_diet_drug_interactions_2017.pdf provides a very detailed description of the known tyramine content of most foods, and is highly recommended. What follows is an abbreviated summary.
  - Dairy products

    - Most cheeses now have low tyramine levels (< 10 mg/kg), whether they are hard, semi-hard, acid-curd or soft. 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. 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. There have been thousands of tyramine estimations performed from cheeses all over the world. Almost all commercial lower priced 'processed' and

'supermarket' cheeses are low in tyramine (always <200 mg/kg, usually in the range of <50 mg/kg) because 'supermarket' type outlets require large quantities of produce (i.e. industrial-scale, not artisan), and long warehouse aging (i.e. more than 3 months) is expensive.

- Processed cheese generally has low levels of tyramine. Ibrahim et al. analyzed 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 higher.

- Non-matured cheeses, yogurt, milk

    - Cheese spreads

        - 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 ifone was to eat a whole tub of it. On the other hand, most spreads are like commercial cream cheeses and contain no tyramine.

    - Fresh non-matured, i.e. unripened/unaged, cheese styles, and yogurt, are always safe because milk itself has no tyramine, e.g. curd styles, fromage frais, mascarpone, cream, ricotta, mozzarella, cottage cheeses, bocconcini. Spizzirri et al. assayed multiple samples, tyramine: 0 mg/kg; Unripened cheeses: 10 samples: tyramine < 0.5 mg/kg. Goat cheese, unripened 'frais' styles, usually tyramine < 5 mg/kg, many 0 mg/kg. Aged goat cheeses: usually low tyramine < 10 mg/kg, but some may be higher, e.g. 70 mg/kg.

- Soy bean products

    - All fermented soy bean products like sauce and paste are prone to have significant tyramine levels. Non-fermented products like (most) tofu have no tyramine. 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 pasteurized. 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. Japanese soy sauce: Maximum tyramine 940 mg/L (i.e. approx. 1 mg/ml). Most samples measured have ranged between 10-200 mg/L. 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 have tyramine levels around 100 mg/L.

- 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, but if it is stored badly or past its 'use by' date when purchased, and then kept in a refrigerator that is not cold enough, it may become risky. Ordinary commercial beef is not usually aged and concentrations of tyramine are likely to be < 10 mg/kg. Fresh meats contain no significant amounts of tyramine. Stored chilled meats are safe (i.e. < 10mg/kg). For example: Beef, stored at –18°C for 178 days, tyramine <4 mg/kg; Chicken, refrigerated for 20 days at 4°C in a domestic refrigerator, tyramine level 3 mg/kg (day 1), 15 mg/kg (day 20); Poultry/duck, insignificant tyramine levels.

- Ground beef is potentially problematic because any contaminant bacteria are mixed into a medium with a large surface area, which may then be sub-optimally stored. Still, assays have found negligible levels of tyramine < 3 mg/kg. 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.

- Pork and fresh pork products have no tyramine. As with all dry cured meat products (as opposed to fermented ones) only low concentrations of tyramine have been observed, so 'Parma ham', pastirma, jamon, prosciutto, coppa etc are all safe. Fermented sausages: concentrations of tyramine depend 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 biogenic amines.

- Preparations of stock cubes, powders, bouillon: these are not prepared by fermentation but are flavoured extracts and reductions, and therefore are unlikely to be high in tyramine. When multiple were tested, none exceeded tyramine 10 mg/kg.

- Fish:
    - levels of both tyramine and histamine may be increased in poorly refrigerated produce. Freshness and low-temperature handling is important, and quality control and screening of imported produce continues to be a powerful force for improving hygiene and handlingmworld-wide. A recent review confirmed low tyramine levels in properly handled raw and processed seafood. Fresh fish usually has less than 5 mg/kg tyramine. Whole and filleted trout kept on ice for up to 18 days, max at 18 days was 7 mg/kg. Frozen fish 1 mg/kg. Chilled fresh and frozen or thawed salmon had a max of 40 mg/kg at the end of shelf life. Smoked salmon dry-salted, traditional smoking, sliced, vacuum-packed stored nine days at 4°C

and 19 at 8°C contains no tyramine.

- Vegetables
    - 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 even banana and avocado, though best to avoid when over-ripe).
    - Preparation of olives may involve bacterial lactic acid fermentation, tyramine levels in olives, and capers are very low.
    - Sauerkraut is made by lacto-fermentation, as are kimchi and traditional pickled cucumbers. These keep for several months, unrefrigerated. In a review of 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.
- 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).
- Alcohol
    - 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.
    - Homemade wines or beers may be risky.
    - Bottled beer is safe if pasteurized; 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: in recent major reviews that covered many hundreds of different wines of all types, almost all had tyramine levels of less than 5 mg/L.
- 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 and 650 mg/kg of tyramine. 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.

- Sourdough bread

  - Sourdough bread differs from normal bread because it utilizes 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 standardized starter cultures (with minimal decarboxylase activity) are used, as is now generally the case with commercial production. However, Artisan producers may utilize cultures with greater decarboxylase activity. Therefore, their products may sometimes contain significant levels of tyramine.

- Summary

  - Minimizing or avoiding the few high-tyramine foods and beverages that do exist can be reliably achieved. Only a few foods can build up the degree of excess tyramine (hundreds of mg/kg) that can greatly raise the BP.

  - A pressor response is in proportion to the amount of tyramine that is consumed, i.e. it is dose-related. That is why it is safe to cautiously test small quantities of some foods, e.g. a favorite cheese or soy sauce.

  - It is not possible to make a general comment about compound foods, e.g. pizza. Such foods can have various ingredients with different tyramine content. Most pizza styles use mozzarella cheese, which has no tyramine, although other cheese styles may be used (e.g., cheddar); these are 'commercial' styles that are stored frozen and are unlikely to be high in tyramine.

  - Special starter cultures that have been deliberately 'engineered' to have no decarboxylating micro-organisms in them, and, therefore, produce no tyramine, are now used in most food production processes. They are used by most cheese-makers (including 'artisan' makers) because they also minimize the formation of undesirable 'off' flavors caused by the proliferation of contaminant organisms and thereby

further lessen any chance of tyramine formation.

- Although very occasional, high-tyramine foods are still encountered outside mainstream food production, for the majority of people eating a typical modern diet there are now very few foods that are likely to contain sufficient tyramine to provoke a problematic pressor response, when consumed in usual healthy amounts. Items that return somewhat higher levels of tyramine (> 250 mg/kg) are ‘savories’ taken in smaller portions (cheeses, salamis, soy sauces) and, therefore, the ‘per serving’ amounts of tyramine remain low. Even a rarely encountered very high tyramine cheese (1000 mg/kg) is, in fact, going to be ‘safe’ for many people (in a healthy portion of 25 g). Since very few cheeses now have tyramine levels of more than 250 mg/kg, healthy portion sizes will be safe for everyone.

- Low dietary tyramine loads mean that almost all those pressor reactions that do occur will be mild (because it is a dose-related effect), only last 1–2 h, and will not require intervention.

Adapted from Gillman, www.psychotropical.info