MDMA

Pharmacodynamics

Neurotoxicity

MDMA’s potential neurotoxicity is undeniable.

There's some evidence that even single doses of Ecstasy (not always MDMA) can produce a significant, albeit subclinical, cognitive deficit in first-time users [1].

Studies using neuroimaging includes [2], [3], [4], [5], [6], [7], [8], [9]. All documenting some deficits in the brain, following presumed MDMA use.

Other nonneuroimaging studies have have other long term damages induced by MDMA; [10]

Heres a stduy that found abstinent users were impaired in memory, verbal fluency, and complex attention; [11]

Here's one that found that even a small, first dose of ecstasy can cause a decline in verbal memory[1].

Here's another that found memory impairments and the researchers believe it is directly caused by Serotonergic neurotoxicty [12].

Here's one that found memory impairments in abstinent users and evidence of PFC dysfunction [13] .

Here's one that found a direct relationship between amount of usage and amount of declarative memory deficit [14].

Here's one that found that heavy users had a weaker blood oxygenation level-dependent response during a working memory task[15].

And not all evidence is limited to just serotonin axons and the SERT. Evidence exists that MDMA damages vital brain structures as well [16]. This study found that the hippocampus in MDMA users literally *shrinks*

Here's one that found diminished hippocampal activation during memory retrieval [17].

here's a case report of a 16 year old who suffered "hippocampal remodelling" after low to moderate use [18].

Here's one that found toxic effects on the thalamus [19].

MDMA induced 5-HT neurotoxicity arises from some of its metabolites, (see later).
Oxidative stress is exacerbated by increasing body temperatures due to a lowering of effectiveness of your body's natural mechanism for protection, antioxidants. Dopaminergic drugs increase body temperature even more. THC helps lower your temps.
Excitotoxicity and tolerance arises from MDMA induced extracellular glutamate release. This binds to your NMDA receptors, opening your ion channels, and allowing calcium to enter your neurons in too high a concentrations. This lowers the effectiveness of your calcium channels, and can even lead to neuronal death if the Ca levels get too high.

Water retention is due to release of vassopressin. Green tea extract can help with this.

The reason your serotonin levels take so long to replenish after use is due to an MDMA induced lowering of tryptophan hydroxylase. This is due to the ring hydroxylated metabolites of MDMA, 2,4,5-trihydroxyamphetamine (THA) and 2,4,5-trihydroxy-N-methylamphetamine (THM). (see figures)

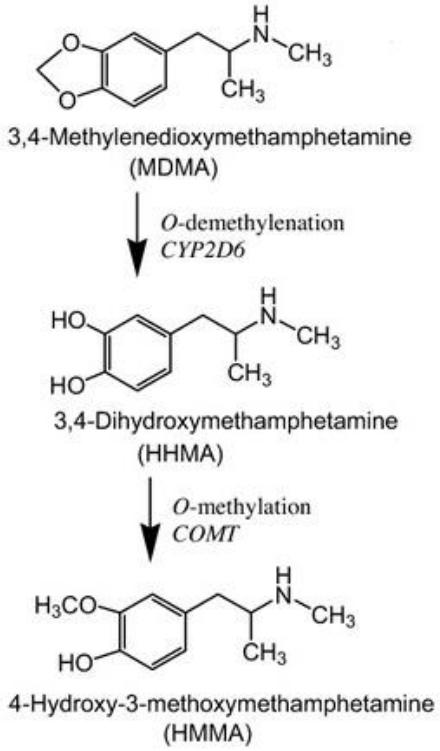
MDMA induced neurotoxicity arises from oxidation of various substances in the brain. There is great debate of which substances are to blame. One theory is that a hepatic metabolite of MDMA, being uptaked into the serotonin axon, gets oxidized into damaging hydroxyl radicals. Another theory is that dopamine is the substance to blame for the oxidation. Another theory is that MDMA itself is reuptaked into the axon, being broken down by MAO-B. More likely is that it is a combination of substances being oxidized into harmful hydroxyl radicals. The common denominator for all evidence to MDMA's neurotoxicity is elevated body temperature. When your body temperature rises, you body's natural process for preventing oxidative stress (antioxidants) becomes less efficient. That lowering of efficiency is exponential. The higher your body temperature gets, the faster reactive oxygen species are created, damaging your brain. Not one single study in the history of MDMA has shown neurotoxocity when body temperature has been kept steady. Pretty conclusive evidence for thermogenesis being the cause of MDMA neurotoxicity. Rats given a known neurotoxic does (20mg/kg, which would be the equivalent of me taking a 264mg dose), who were kept in a room at 20-24C, showed NO neurotoxicity in any part of the brain. Rats given the same dosage, but kept in a room 26-30C showed neurotoxicity in all regions of the brain affected by MDMA. A 2 degree Celsius rise in ambient temperature was all it took to turn no damage, to neurotoxicity in multiple parts of the brain[20].

Metabolism

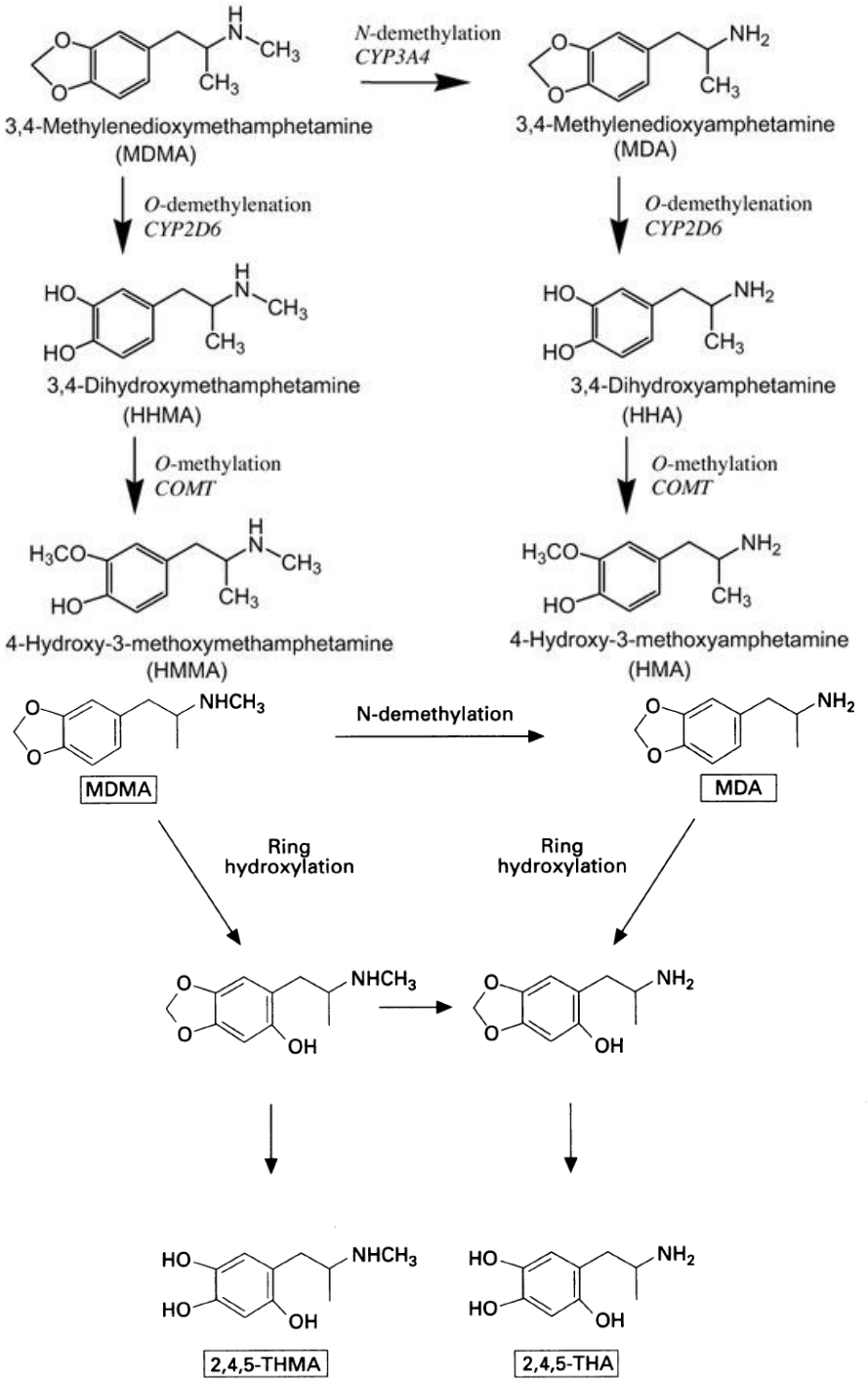
The human cytochrome CYP450 is responsible for the metabolism of MDMA. The primary enzyme responsible is CYP2D6, using O-demethylation. This process adds two hydrogen atoms to the two open oxygen atoms in MDMA to create HHMA. Let's look at the structure for a minute.

MDMA is 3,4-methylenedioxy-N-methylamphetamine
HHMA is 3,4-dihydroxy-N-methylamphetamine
So your CYP2D6 enzyme added two hydrogen atoms to the methylenedioxy structure to create a dihydroxy structure. Once it's been o-demethylated to HHMA, it is no longer active like MDMA is. HHMA can then be 0-methylated further to HMMA, or 4-hydroxy-3-methoxy-N-methylamphetamine.

This is the primary route of metabolism.



MDMA is primarily metabolized by CYP2D6. However, a portion of your dose (~10%, more accurately between 7-15 %) is also metabolized by your CYP3A4 enzyme using N-demethylation. The product of this reaction is MDA, or 3,4-methylenedioxyamphetamine. Your CYP3A4 enzyme changed the methyl group at the N position, and not the O position. This modified the methyl group into an amine group. We are now left with MDMA's more neurotoxic derivative in our blood .



While there is good evidence that CYP2D6 is the primary metabolic pathway for MDMA, hydroxlyation is possible at all 3 ring positions. Interestingly, CYP3A4 inhibition would lead to lower levels of ring-hydroxlated MDA metabolites, which I think (largely due to their similarity to 6-hydroxydopamine) are more likely candidates for neurotoxicity than the corresponding MDMA metabolites.

MDA is then metabolized in the exact same manner MDMA was, o-demetylation by CYP2D6. So we add two hydrogen atoms to the O position to create HHA, or 3,4-dihydroxyamphetamine. So we essentially end up with HHMA with an amine group at the N position instead of a methyl group. It can also be o-methylated further (like HHMA) into HMA 4-hydroxy-3-methoxyamphetamine. Same thing as HMMA, just with an amine group instead of the methyl group.

MDMA and MDA injected directly into the brain have been shown to **NOT** be neurotoxic[22]. [23] showed that individuals with lower CYP2D6 did not show lower neurotoxicity. In fact, they showed slightly higher. It may have led to some deaths as well[24].

A person that has a genetic condition resulting in lower CYP2D6 enzyme is going to have what happen to their MDMA? A greater percentage will be N-demethylated to MDA by CYP3A4. This is going to lead to what higher HHA serum levels. HHA is a known neurotoxin[25].

So MDMA and MDA injected directly into the brain show no neurotoxicity. Individuals with lower CYP2D6 enzyme show higher levels of neurotoxicity. This leads me to believe that HHMA is not the primary culprit (probably still a factor though).
MDA has been shown to be much more neurotoxic than MDMA. MDA is NOT neurotoxic when directly injected into the brain. MDA cannot be metabolized into HHMA, but is directly metabolized to HHA. This could lead one to hypothesize that MDA is the cause of MDMA's neurotoxicity through metabolism to HHA (Also known as alpha-methyldopamine) [26].

[28] showed that body temperature drastically affected metabolism to MDA. So temperature plays a role here as well.

On half life of metabolites:
There is going to be more first-pass metabolism if you take it orally. Intranasal and rectal will have less. It also depends on your polymorphisms. CYP2D6 and CYP3A4 both matter. I would say that the half life of the metabolites is between 10-15 hours after ingestion.
[27]

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MDMA (5 mg kg-1, i.p.) was without effect on brain 5-HT content. A single dose of MDA (5 mg kg-1, i.p.) produced a major (approximately 40%) loss of 5-HT content of cortex and hippocampus 7 days later[23].

Indeed, 5-(N-acetylcystein-S-yl)-R-MeDA is more than 2 orders of magnitude more potent than 5-(glutathion-S-yl)-RMeDA (14, 15). Intrastriatal administration of 5-(Nacetylcystein- S-yl)-R-MeDA, **at a dose as low as 7 nmol, produces a 50% reduction in striatal 5-HT concentrations**, approximately equivalent to the effects of 23.25 ímol MDA (93 ímol/kg s.c. in rats weighing 250 g) kilde?.)

Mitigation of neurotoxicity

SSRI, day after

The main theory is that the SSRI will bind to your SERT and prevent oxidative substances from being re-uptakes into your serotonin neurons. I do believe this to be the case, but not the whole story. What else are SSRIs potent inhibitors of? CYP450 enzymes. Now most SSRIs are only potent inhibitors of CYP2D6. However, the primary metabolite of fluoxetine, norfluoxetine, also inhibits CYP3A4. So not only does taking fluoxetine bind to your SERT, it also inhibits the metabolism of MDMA to it's toxic metabolites.

ESSENTIALS!

Grapefruit Juice

Grapefruit juice inhibits CYP3A4. CYP3A4 is the enzyme in your liver than can metabolize the N-methyl group off the MDMA molecule. MDMA without the N-methyl group is MDA. MDA can then be metabolized by CYP2D6 by stripping off an oxygen atom from the methylenedioxy functional group. This is what creates the harmful metabolite.
These substances are CYP3A4 inhibitors. I knew that CYP3A4 metabolized part of my dose to MDA. I knew it was more neurotoxic, which is why I did this. However, I did not connect the dots as to why it was more neurotoxic.
Many postulated it was because of MDA's higher affinity for dopamine. However, why then did direct injections of it in the brain not cause neurotoxicity? If it was dopamine being re-uptaked by your SERT that was causing the damage, it would still be present when MDMA or MDA was directly injected into the brain. In fact, it would be higher. Yet we saw NO neurotoxicity.
Others were skeptical because the metabolism to HHA was only seen in rats. However, [25] proved it happened in humans too.

5-ttp

MDMA and MDA are ring-hydroxylated to THM and THA respectively.
MDMA also induces a lowering of TPH, or tryptophan hydroxylase. This is due to the ring hydroxylated metabolites of MDA called 2,4,5-trihydroxyamphetamine (THA) and 2,4,5-trihydroxy-N_methylamphetamine (THM) [21].

TPH is the enzyme that creates 5-HTP from tryptophan in your diet. So you supplement 5-HTP the week after because it skips that step, and allows your body to replenish it's serotonin stores.

Do not preload with 5-HTP. It can lessen the effects by causing your 5-HT receptors to down-regulate. Post loading is good, and I do it every time. Always take EGCG with your 5-HTP.

ALA

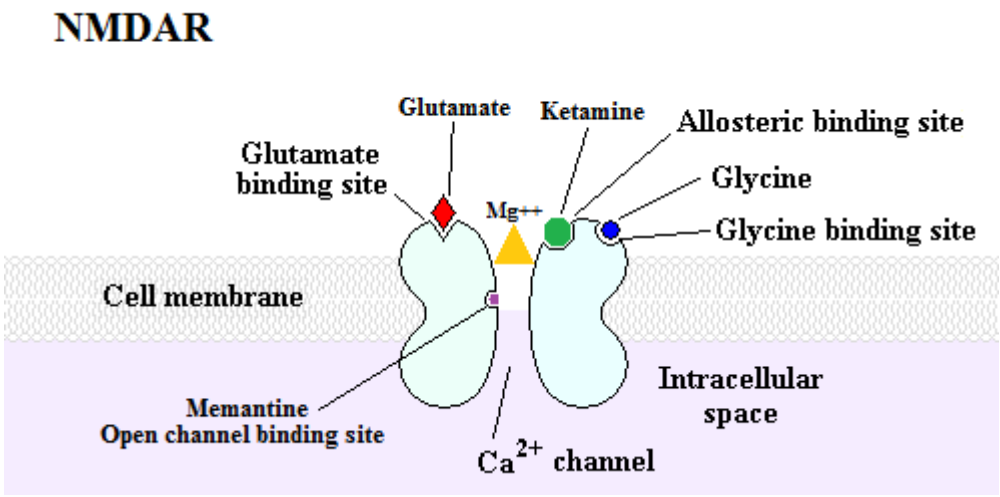
This is one that everyone should be taking. It is a powerful antioxidant that scavenges reactive oxygen and nitrogen species [29]. It also has a nice benefit of regenerating other vitamins, like C, after redox cycling. It exists in two enantiomers, R-ALA and S-ALA. R-ALA is the biologically active isomer that we are looking for. Most supplements are racemic, or a mix of both. Racemic ALA does not reach as high of plasma levels as R-ALA, nor does it stay in the blood as long. It's half life is very short, ~30min. If that is all you can find, it's much better than nothing. R-ALA by itself is very unstable, and is not suitable for supplementation. This is where bonding it to sodium comes into play. Na-R-ALA, or sodium R alpha lipoic acid, allows for stable delivery of just the dextrorotory isomer of ALA. Here is a study on the benefits of Na-R-ALA. And here is the study showing that ALA prevented MDMA induced neurotoxicity, even though body temperatures still rose [30].

Dosage and time schedule:
Racemic ALA- 200mg before MDMA dose and every hour of roll.
Na-R-ALA- 100mg before and every 2 hours of roll

Magnesium

MDMA induces a release of extracellular glutamate in the hippocampus. Glutamate is the body's primary excitatory neurotransmitter. It binds to NMDA receptor sites, along with glycine, opening the ion channels and allowing calcium to enter the neuron. This is how the brain sends cascading electrical signals. When the ion channels open for too long or too frequently, calcium concentrations can become too high in the neuron. This can lower the effectiveness of your ion channels, or can even cause neuronal death. Magnesium is the substance your body uses to block the channel in a voltage-dependent manner. This means that the ion channel will not allow Ca2+ to pass, even if glutamate and glycine are bound to their receptor sites. However, once the neuronal membrane's electrical potential rises to an excited state, the Mg molecule will clear the channel and allow for normal operation. Most people

are deficient in magnesium as it is. Supplementing a highly bioavailable magnesium supplement will give your body the substance it needs to naturally protect itself from excitotoxicity



There are a number of different types of magnesium supplements. Some are not absorbed very well, other are. The most common form, oxide, is one of the worst. This is where the concept of chelation comes into play. Magnesium is a substance the readily binds to insoluble salts in the stomach and intestines. This makes it hard to absorb. However, if you chelate the magnesium molecule to a soluble amino acid, it prevents it's binding to insoluble salts, as well as opening up the possibilities for active transport. This means that fully chelated magnesium is absorbed much better by the body. There are a number of different Mg/amino acid combinations. My favorite is magnesium glycinate. This is Mg chelated to a glycine molecule.
Dosage and time schedule:
Magnesium Glycinate- 2,000mg (200mg elemental Mg) 6 hours before, 1 hour before, and during.

Vitamin C

This is a widely known antioxidant. It will help scavenge any reactive oxygen species that get created. It has been shown to prevent MDMA induced hepatotoxicity [31]. It has also been shown to mitigate neurotoxicity as well [32]. It will also raise stomach acidity, which will slow absorption of MDMA through the stomach and intestines. I also drink it throughout the night, raising my urinary acidity. This allows me to

excrete much of the MDMA in my urine before it metabolizes to harmful substances.
Dosage and time schedule:
(1,000mg vitamin C) 1 hour before and during

Taking Bicorabonate to raise stomach PH 30 min before ingesting MDMA will increase absorption.

Grape seed extract

GSA is a supplement high in vitamin E and flavonoids. Vitamin E deficiency has been shown to increase the severity of MDMA induced neurotoxicity [33]. Also, flavonoids are potent antioxidants that will help protect against lipid oxidation and reactive oxygen species.

Dosage and time schedule:
Grape seed extract- 100mg before and during

Grapefruit juice

My other post spoke about CYP3A4 metabolizing MDMA to MDA using N-demethylation. MDA is MUCH more neurotoxic than MDMA, and I spoke to why before. I am not going to rehash the specifics here, but there is no doubt that any MDA in your system is bad for you. The furanocoumarins present in grapefruit juice are potent CYP3A4 inhibitors. This a 90% reduction in CYP3A4 metabolism after grapefruit juice ingestion. This study measured metabolism to MDA in humans. How much of your MDMA dose gets metabolized to MDA depends on a number of different factors, like dose, re-dosing schedule, body temperature, etc. Drinking grapefruit juice will drastically inhibit this metabolism. Your MDMA plasma levels will be higher when taking GFJ, so be aware of that when selecting dosages. It also has vitamin C and will increase stomach/intestinal/urinary acidity. This will help excrete MDMA in urine unmetabolized.

Dosage and time schedule: Drink some in the morning, an hour before drop, and some later in the night.

Suggested suppkements::
Acetyl-L-carnitine- Is synergistic with alpha lipoic acid, and protects against oxidative stress. Has been shown to prevent MDMA induced neurotoxicity[34].

Dosage and time schedule:
ALCAR- 500mg before and during

- **Green Tea Extract (EGCG)**- Is a potent antioxidant and diuretic. It will help with the urinary retention arising from MDMA induced vasopressin release [35].

Dosage and time schedule:
Green tea extract- 400mg before and during

- **5-HTP**- 5-HTP is the direct precursor to serotonin (5-HT). It is created from tryptophan in your diet using the enzyme tryptophan hydroxylase (TPH). MDMA can reduce TPH levels for weeks after use[21]. This will make it harder for your body to produce the necessary 5-HT from normal dietary sources alone. Since 5-HTP does not need TPH, supplementing it the few days following your roll will help you body restore it's 5-HT levels. 5-HTP can pass your blood brain barrier, while 5-HT cannot. This means that when you supplement 5-HTP, you want to make sure it gets converted to 5-HT in your brain and not your periphery. The enzyme that converts 5-HTP to 5-HT is aromatic L-amino acid decarboxylase. It is found in your stomach and periphery, as well as your brain. This means that we have to inhibit it, so that your 5-HTP has time to pass your blood brain barrier. EGCG is an inhibitor of L-amino acid decarboxylase (Also known as DOPA decarboxylase). ALWAYS take EGCG with your 5-HTP to ensure that your brain is getting the serotonin, and not your periphery. Excess 5-HT in the periphery can cause heart valve damage.
    - Only a small portion of your EGCG dose will pass your blood brain barrier. This is enough to exert it's antioxidant activity, but not enough to inhibit 5-HT production. However, blood levels of EGCG will be much higher, and will inhibit enzymes in the periphery.
    - However even after continuous administration of EGCG until 24 h, levels of the compound in brain tissue reaches **5–10% of its blood levels**. This suggests that a very high plasma concentration is needed for EGCG to reach a reasonable therapeutic level in brain

- A study more relevant for human exposure to epicatechins followed six subjects (scheduled for lumbar puncture) after the ingestion of a 300 mL boiling water infusion of 7 g of green Kenyan tea (150). The average intake of (-)-epicatechins was 53 µmol of epicatechin, 149 µmol of epigallocatechin, 206 µmol of epigallocatechin- 3-O-gallate, and 97 µmol of epicatechin-3-Ogallate. After 1 h, plasma levels of the epicatechins were readily detectable with total epicatechin concentrations amounting to about 1.6 µM; **however, nothing was found in cerebral spinal fluid.**
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- Also, EGCG's effects on the brain are largely due to it's glucuronide and 30-O-methyl glucuronide forms. This means that the EGCG's effects on the brain are not necessarily all from EGCG in it's normal form. So even though only a little passes the BBB unchanged, it can still provide neuroprotection via it's metabolites.
- Here is the study showing that EGCG inhibits aromatic L-amino acid decarboxylase.

Dosage and time schedule:
5-HTP (with 400mg EGCG)- 100mg before bed for 3-7 days following MDMA use

- **Melatonin**- Melatonin is created from serotonin. Your body uses it to control sleep/wake cycles. It is also a very powerful antioxidant. After using MDMA, your serotonin levels will be low, and your melatonin levels will be affected. Taking a melatonin supplement before bed will help you sleep, but will also help scavenge any oxidative substances your other antioxidants have missed.
- Interestingly enough, melatonin is also quite effective at lowering body temperature , albeit at fairly high dosages it could be used during MDMA, if body temperature is a problem [36].

Dosage and time schedule:
Melatonin- 5-10mg before bed (Keep in mind we are using a higher dose here for it's antioxidant properties. Normal dosages should be .5mg to 1mg.)

- **CoQ10 or PQQ**- When your NMDA receptors open and allow Ca2+ to influx into

the neuron, that calcium must then be pumped back out of the neuron to bring it back down to resting potential. Protein pumps are what force the Ca2+ back into the extracellular space. To do this, they need andenosine triphosphate (ATP). CoQ10 is used by your body to synthesize ATP, which will allow your protein pumps to be able to expel the excess Ca2+ more efficiently. This will protect your neurons from exitotoxicity.

Dosage and time schedule:
CoQ10- 100mg before

Don't forget water and electrolytes, and KEEP YOUR BODY TEMPERATURE DOWN.

Mixing MDMA and other drugs

On methylphenidate: Could lead to increased neurotoxicity, by raising body temperatures. It might also dampen your roll. Cocaine affects your roll by binding to the SERT and stopping the MDMA induced release of 5-HT. Ritalin works in a similar fashion to cocaine. However, I am not 100% sure of it's affinities in relation to MDMA. It would be safer than taking amphetamine or more MDMA, though.

Studies have shown that 200mg MDMA in one dose produces lower toxicity than 200mg spread over 4 doses. This is to do with the metabolism of MDMA by CYP2D6. Upon first dose, it binds to CYP2D6 and inhibits it. This causes more to be metabolized by CYP3A4 to MDA. If you are going to do it, make sure you keep drinking grapefruit juice. That will inhibit CYP3A4.

this study, though. It showed that NAC was neuroprotective when administered with MDMA. Jury is still out for me.
http://bcn.iums.ac.ir/browse.php?a_id=198&slc_lang=en&sid=1&ftxt=1

When supps are marked as before but not specified. It should be taken 2-1 hours before.

MDMA + alcohol: nogo. Increases neurotoxicity, by mechanism not limited to acute hyperthermia [37].

Discussion on non-human animal studies relating to humans.

the proportion of metabolites formed in normal metabolism of MDMA by rats and humans varies. Humans produce ≈2-3 times less (10% vs 30%) MDA (3, 4-methylenedioxyamphetamine) than rats. MDA is recognised as the principle metabolite responsible for neurotoxic damage. Figure 3, attached in supplementary material is a schematic showing proposed pathways of metabolism of MDMA to MDA (Capela et al 2006). An additional consideration is the absence of the auto-inhibitory effects of CYPD26, a cytochrome enzyme largely responsible for processing xenobiotics, including metabolism of MDMA. (Green et al. 2012) Rats instead have a homologous but functionally distinct enzyme – CYPP2D1, which displays no auto-inhibition. (Malpass et al. 1999) (Maurer et al. 2000) This dual metabolism and inhibition by CYP2D6 in humans means the associated kinetics are non-linear. This is not true for rats, where the relationship remains linear until extremely high doses, and starts to diverge only because of saturation of clearance by the liver (de la Torre et al. 2004). Comparisons in this way between humans then, only really make sense at doses up to around 2.5mgkg-1, and move apart rapidly after this. Unfortunately, recreational doses in human use often exceed 2.5mgkg-1.
Plasma protein binding represents the “truest” representation of pharmacologically active drug. Only one study on plasma protein binding in MDMA has been carried out, and this was 20 years ago in dogs. (Garrett et al. 1991)
In comparing rats and human data, we encounter the final problem; MDMA's LD50 in humans is thought to be roughly 1000ngMl-1. In studies carried out to induce neurotoxicity in rats, it has usually been necessary bring plasma levels to over 1500-2000ngml1-1, several times. Non-equivalence in this data set poses serious problems for cross-species comparability.

The non-linear kinetics in humans still fits within my theory. Included with the rat studies, I read through primate and even a human study. The more I read, the more my theory keeps falling into place. It has also clarified some things for me. I postulated that rats showed greater 5-HT damage because they had less efficient delivery systems for antioxidants. I now believe that still may be the case, but it is more to do with their CYP2D1 enzyme being the primary metabolic pathway for MDMA to MDA. Not only that, but we always thought that temperature increases led to greater 5-HT neurotoxicoty because it reduced the efficiency of our antioxidants systems. However, after reading the full study (Banks et al. 2007), temperature

increases led to greater metabolism to MDA. Also, re-dosing has been a known path to neurotoxicity. The study (Torre Farre 2004) showed that re-dosing in primates led to a 200% increase in MDA levels, up to 18% of the total MDMA dose. This proves that the metabolic pathway to MDA is there in primates, as well as providing reasoning for the higher neurotoxicicty observed when re-dosing. It all fits perfectly within my theory! I've been going back and forth with the Redditor who is getting me the studies via private message. In that time I have gathered much more evidence that MDA is the cause.

MDMA is N-Demethylated by the human enzyme CYP3A4 to MDA. Temperature increases, as well as re-dosing intervals, increase this metabolic pathway, leading to as much as 18% of total MDMA dosage becoming MDA in primates. MDA is then either O-Demethylated to 3,4-dihydroxyamphetamine **(HHA)** via the human enzyme CYP2D6, or ring-hydroxylated to 2,4,5-trihydroxyamphetamine **(THA)**.
HHA is very unstable, and rapidly conjugates with glutathione into 2,5-Bis-(glutathion-S-yl)-alpha-methyldopamine. This is the substance that causes 5-HT neurotoxicity in the brain. Even if COMPT is inhibited, causing less HHA to be metabolized to HMA, HHA levels DO NOT rise. This also leads to incresed 5-HT damage. This proves that HHA is unstable, and is rapidly conjugated by glutathione. If it was not being conjugated, an inhibition of COMPT would lead to an increase in HHA serum levels, as well as an increase in HHA in the urine. It does not.
The other piece of this puzzle is THA. The ring-hydroylated metabolite of MDA, administered by itself, led to a 92% decrease in tryptophan hydroxylase (TPH) after 7 days. This explains MDMA's reduction in TPH the 2 weeks following use, consequently causing serotonin stores to not replenish in a timely manner. That does not mean that MDMA itself is not to blame as well. The ring-hyroxylated metabolite of MDMA, 2,4,5-trihydroxy-N-methylamphetamine (THM), also reduced TPH. However, it only reduced it by 48%. There is no doubt, MDA is much more damaging to the serotonin system.
Now you may be thinking, what about HHMA, HMMA, and their conjugates? They are probably leading to toxicity as well, right? NOPE! The study (Mueller et al. 2004) proved that neither HHMA, HMMA, nor any of their conjugates pass the blood brain barrier. Furthermore, they injected them directly into the brain, causing ZERO elevation in 5-HT damage. This proves that the N-methylated metabolites of MDMA directly ARE NOT neurotoxic. However, the study (Carvalho et al.) did prove that HHMA is hepatotoxic. They also proved that abscorbic acid prevents this

hepatoxicity. So the N-methylated metabolites are still toxic, but damage is limited to the periphery.
Take this information, along with the fact that MDMA nor MDA are neurotoxic when directly injected in the brain, and my theory is the only thing left. 2,5-Bis-(glutathion-S-yl)-alpha-methyldopamine and 2,4,5-trihydroxyamphetamine (THA) are the two substances that are solely responsible for MDMA induced neurotoxicity. They also happen to only be possible if MDMA is N-demethylated to MDA. This is why MDA is much more neurotoxic than MDMA when administered alone. It's also why re-dosing and temperature increases lead to more 5-HT system damage. MDA is the asshole in the room. Inhibit CYP3A4 to prevent the neurotoxic metabolites from being created!

There is a lot more I have to say about increased extracellular glutamate, NMDA and AMPA receptors, as well as dopamine toxicity. Also, my findings here are aggregated from many studies, by many different labs, from many different perspectives, over the last 30 years. When an issue would arise in one study, I would look to other studies to find possible clarifications. I did not go into this with any preconceptions, but rather an open mind to try and find the truth. I made every attempt to eliminate selections bias, and I have nothing to gain professionally from my theory. If I ended up finding that there was no way to mitigate neurotoxicity, then c'est la vie.

Massive doses in some animal experiments.

Other

Dopamine and neurotoxicity? [38]

1. Schilt, T., et al., *Cognition in novice ecstasy users with minimal exposure to other drugs: a prospective cohort study.* Arch Gen Psychiatry, 2007. **64**(6): p. 728-36.

2. Buchert, R., et al., *Long-Term Effects of "Ecstasy" Use on Serotonin Transporters of the Brain Investigated by PET.* Journal of Nuclear Medicine, 2003. **44**(3): p. 375-384.
3. Reneman, L., et al., *Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (mdma or "ecstasy"): Preliminary findings.* Archives of General Psychiatry, 2001. **58**(10): p. 901-906.
4. Cowan, R.L., D.M. Roberts, and J.M. Joers, *Neuroimaging in human MDMA (Ecstasy) users.* Ann N Y Acad Sci, 2008. **1139**: p. 291-8.
5. Kish, S.J., et al., *Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/[(11)C]DASB and structural brain imaging study.* Brain, 2010. **133**(Pt 6): p. 1779-97.
6. Bauernfeind, A.L., et al., *Human Ecstasy use is associated with increased cortical excitability: an fMRI study.* Neuropsychopharmacology, 2011. **36**(6): p. 1127-41.
7. Erritzoe, D., et al., *IN vivo imaging of cerebral serotonin transporter and serotonin2a receptor binding in 3,4-methylenedioxymethamphetamine (mdma or "ecstasy") and hallucinogen users.* Archives of General Psychiatry, 2011. **68**(6): p. 562-576.
8. Thomasius, R., et al., *Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users: the longitudinal perspective.* Journal of Psychopharmacology, 2006. **20**(2): p. 211-225.
9. Gerra, G., et al., *Long-lasting effects of (±)3,4-methylene-dioxymethamphetamine (Ecstasy) on serotonin system function in humans.* Biological Psychiatry, 2000. **47**(2): p. 127-136.
10. Kelly, P.A.T., *Does recreational ecstasy use cause long-term cognitive problems?* Western Journal of Medicine, 2000. **173**(2): p. 129-130.
11. Yip, J.T.H. and T.M.C. Lee, *Effect of ecstasy use on neuropsychological function: a study in Hong Kong.* Psychopharmacology, 2005. **179**(3): p. 620-628.
12. Morgan, J.M., *Memory deficits associated with recreational use of "ecstasy" (MDMA).* Psychopharmacology, 1999. **141**(1): p. 30-36.
13. Quednow, B.B., et al., *Memory deficits in abstinent MDMA (ecstasy) users: neuropsychological evidence of frontal dysfunction.* Journal of Psychopharmacology, 2006. **20**(3): p. 373-384.
14. Blagrove, M., et al., *Procedural and declarative memory task performance, and the memory consolidation function of sleep, in recent and abstinent ecstasy/MDMA users.* Journal of Psychopharmacology, 2011. **25**(4): p. 465-477.
15. Daumann, J., et al., *Cerebral activation in abstinent ecstasy (MDMA) users during a working memory task: a functional magnetic resonance imaging (fMRI) study.* Cognitive Brain Research, 2003. **16**(3): p. 479-487.
16. den Hollander, B., et al., *Preliminary evidence of hippocampal damage in chronic users of ecstasy.* Journal of Neurology, Neurosurgery & Psychiatry, 2012. **83**(1): p. 83-85.
17. Daumann, J., et al., *Memory-related hippocampal dysfunction in poly-drug ecstasy (3,4-methylenedioxymethamphetamine) users.* Psychopharmacology, 2005. **180**(4): p. 607-611.
18. Nifosì, F., et al., *Hippocampal remodelling after MDMA neurotoxicity: A single case study.* The World Journal of Biological Psychiatry, 2009. **10**(4-3): p. 961-968.
19. de Win, M.M.L., et al., *Neurotoxic effects of ecstasy on the thalamus.* The British Journal of Psychiatry, 2008. **193**(4): p. 289-296.
20. Malberg, J.E. and L.S. Seiden, *Small Changes in Ambient Temperature Cause Large Changes in 3,4-Methylenedioxymethamphetamine (MDMA)-Induced Serotonin Neurotoxicity and Core Body Temperature in the Rat.* The Journal of Neuroscience, 1998. **18**(13): p. 5086-5094.

21. Elayan, I., et al., *Short-term effects of 2,4,5-trihydroxyamphetamine, 2,4,5-trihydroxymethamphetamine and 3,4-dihydroxymethamphetamine on central tryptophan hydroxylase activity.* J Pharmacol Exp Ther, 1993. **265**(2): p. 813-8.
22. Esteban, B., et al., *3,4-Methylenedioxymethamphetamine induces monoamine release, but not toxicity, when administered centrally at a concentration occurring following a peripherally injected neurotoxic dose.* Psychopharmacology, 2001. **154**(3): p. 251-260.
23. Colado, M.I., J.L. Williams, and A.R. Green, *The hyperthermic and neurotoxic effects of 'Ecstasy' (MDMA) and 3,4 methylenedioxyamphetamine (MDA) in the Dark Agouti (DA) rat, a model of the CYP2D6 poor metabolizer phenotype.* Br J Pharmacol, 1995. **115**(7): p. 1281-9.
24. Gilhooly, T.C. and A.K. Daly, *CYP2D6 deficiency, a factor in ecstasy related deaths?* Br J Clin Pharmacol, 2002. **54**(1): p. 69-70.
25. Perfetti, X., et al., *Neurotoxic thioether adducts of 3,4-methylenedioxymethamphetamine identified in human urine after ecstasy ingestion.* Drug Metab Dispos, 2009. **37**(7): p. 1448-55.
26. Miller, R.T., S.S. Lau, and T.J. Monks, *2,5-bis-(Glutathion-S-yl)-α-methyldopamine, a putative metabolite of (±)-3,4-methylenedioxyamphetamine, decreases brain serotonin concentrations.* European Journal of Pharmacology, 1997. **323**(2–3): p. 173-180.
27. Banks, M.L., et al., *Ambient temperature effects on 3,4-methylenedioxymethamphetamine-induced thermodysregulation and pharmacokinetics in male monkeys.* Drug Metab Dispos, 2007. **35**(10): p. 1840-5.
28. Baumann, M.H., et al., *Effects of dose and route of administration on pharmacokinetics of (+ or -)-3,4-methylenedioxymethamphetamine in the rat.* Drug Metab Dispos, 2009. **37**(11): p. 2163-70.
29. Packer, L., E.H. Witt, and H.J. Tritschler, *Alpha-lipoic acid as a biological antioxidant.* Free Radical Biology and Medicine, 1995. **19**(2): p. 227-250.
30. Aguirre, N., et al., *Alpha-lipoic acid prevents 3,4-methylenedioxy-methamphetamine (MDMA)-induced neurotoxicity.* Neuroreport, 1999. **10**(17): p. 3675-80.
31. Carvalho, M., et al., *The toxicity of N-methyl-α-methyldopamine to freshly isolated rat hepatocytes is prevented by ascorbic acid and N-acetylcysteine.* Toxicology, 2004. **200**(2–3): p. 193-203.
32. Shankaran, M., B.K. Yamamoto, and G.A. Gudelsky, *Ascorbic acid prevents 3,4-methylenedioxymethamphetamine (MDMA)-induced hydroxyl radical formation and the behavioral and neurochemical consequences of the depletion of brain 5-HT.* Synapse, 2001. **40**(1): p. 55-64.
33. Johnson, E.A., et al., *d-MDMA during vitamin E deficiency: effects on dopaminergic neurotoxicity and hepatotoxicity.* Brain Res, 2002. **933**(2): p. 150-63.
34. Alves, E., et al., *Acetyl-l-carnitine provides effective in vivo neuroprotection over 3,4-methylenedioximethamphetamine-induced mitochondrial neurotoxicity in the adolescent rat brain.* Neuroscience, 2009. **158**(2): p. 514-523.
35. Wolff, K., et al., *Vasopressin and oxytocin secretion in response to the consumption of ecstasy in a clubbing population.* J Psychopharmacol, 2006. **20**(3): p. 400-10.
36. Dollins, A.B., et al., *Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance.* Proc Natl Acad Sci U S A, 1994. **91**(5): p. 1824-8.
37. Izco, M., et al., *Binge ethanol administration enhances the MDMA-induced long-term 5-HT neurotoxicity in rat brain.* Psychopharmacology, 2007. **189**(4): p. 459-470.

38. Johnson, M.P., X. Huang, and D.E. Nichols, *Serotonin neurotoxicity in rats after combined treatment with a dopaminergic agent followed by a nonneurotoxic 3,4-methylenedioxymethamphetamine (MDMA) analogue.* Pharmacology Biochemistry and Behavior, 1991. **40**(4): p. 915-922.