Methamphetamines (MA) and Psychosis

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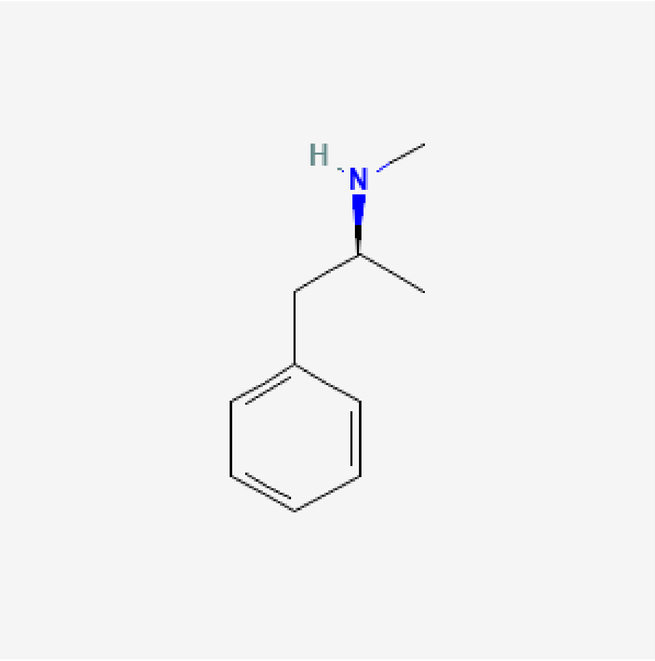
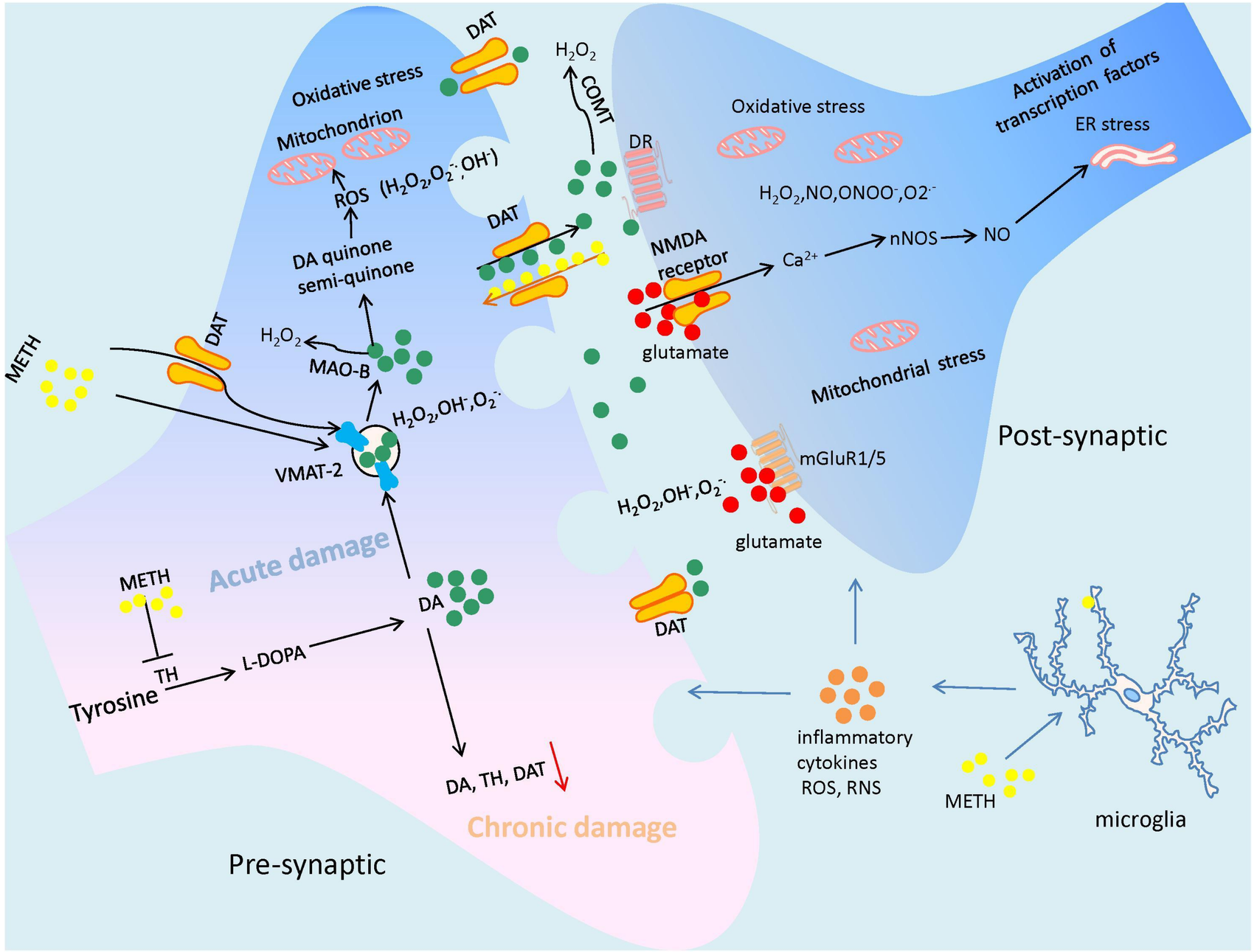
What is methamphetamine (MA)?



- Class: Amphetamines
  - Amino group has the addition of a methyl group
- CNS Stimulant, Appetite Suppression
- MOA: indirect agonists for dopamine, norepinephrine, and serotonin receptors (methamphetamine substitutes for monoamines at DAT, NET, and SERT, as well as reverses monoamine storage in vesicles by VMAT-2)
- Half-Life: 10-12 hours
- Metabolism: Liver, including CYP2D6 (so 2D6 inhibitors can potentially prolong clearance)

https://pubchem.ncbi.nlm.nih.gov/compound/Methamphetamine



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Illicit Methamphetamine Use

US: 1.2 million last year incidence, 440k last month incidence

Particularly high incidence amongst rural Americans, Hispanic, MSM groups

Police study: blood levels ranged from from 15 ng/mL to 1600 ng/mL, median 190 ng/mL. Compared to 10-110ng/mL in prescribed Adderall XR use.

Dose-Dependent Effects: 5-30mg —>arousal, positive mood, acutely improved attention and motor coordination, increased cardiovascular output. But >50mg—>psychosis, cardiovascular complications

Glasner-Edwards S, Mooney LJ. Methamphetamine psychosis: epidemiology and management. CNS Drugs. 2014 Dec;28(12):1115-26. doi: 10.1007/s40263-014-0209-8. PMID: 25373627; PMCID: PMC5027896.

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Cruickshank CC, Dyer KR. A review of the clinical pharmacology of methamphetamine. Addiction. 2009 Jul;104(7):1085-99. doi: 10.1111/j.1360-0443.2009.02564.x. Epub 2009 Apr 29. PMID: 19426289.

MA-Induced Psychosis

- 40% of methamphetamine users may experience transient psychosis during intoxication and/or withdrawal
- Persecutory delusions, auditory, **visual (46.5%) and tactile (including formication)** (21.3%) hallucinations, ideas of reference, disorganized speech all very common
- In chronic methamphetamine users, psychotic symx 5x more likely when using vs not using
  - 48% had psychosis when using daily for 16 days or more, with no polysubstance use

McKetin R, Lubman DI, Baker AL, Dawe S, Ali RL. Dose-related psychotic symptoms in chronic methamphetamine users: evidence from a prospective longitudinal study. JAMA Psychiatry. 2013 Mar;70(3):319-24. doi: 10.1001/jamapsychiatry.2013.283. PMID: 23303

Chen CK, Lin SK, Sham PC, Ball D, Loh EW, Hsiao CC, et al. Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis. Psychol Med. (2003) 33:1407–14. doi: 10.1017/S0033291703008353

So is this a Substance-Induced Psychotic Disorder?

DSM Criteria

Substance-induced psychotic disorder is diagnosable when the following symptoms are present:

(1) Presence of prominent hallucinations or delusions;

(2) Hallucinations or delusions develop during, or soon after, intoxication or withdrawal from a substance or medication known to cause psychotic symptoms;

(3) Psychotic symptoms are not actually part of a psychotic disorder (such as schizophrenia, schizophreniform disorder, schizoaffective disorder) that is not substance-induced (i.e., if psychotic symptom onset was prior to substance or medication use, or persists longer than one month after substance intoxication or withdrawal, then another psychotic disorder is likely);

(4) Psychotic symptoms do not only occur during a delirium.

A Common Scenario

Emergency Psychiatry

- Young male comes in on emergency detention with agitation, persecutory delusions, auditory and visual hallucinations and with disorganized speech
- Collateral and UDS great if you can get them, often can’t
- De-escalatory efforts, lights off, low noise, low-stim
  - PRN antipsychotic and benzodiazepine if needed for safety
- Wait it out, metabolize, admit if necessary for further metabolization while dispo planning and ensuring no safety threat
- Usually…they get clearer and clearer, you get more info, by day 3 ED is expiring and no acute safety threat, discharged
- But sometimes…

Residual Psychosis?

- Instead, psychosis remains very prominent 5, 6, 7 days later, with or without agitation that may necessitate further PRNs
  - *If prolonged psychosis following meth use, important to also consider other causes like delirium/encephalopathy due to underlying medical illness, other substance withdrawal (especially alcohol)
- Contact finally established with family. No personal or family hx of primary psychosis, though family thinks he's been "very unusual" for a couple years while he has been using drugs
- "Will he ever get better?"

Chronic MA-Induced Psychosis

- There may be a “long tail” of residual psychosis. For most of these patients, a majority of their psychotic symptoms will resolve within 1 month
- The rates of continued psychotic symptoms beyond that appears variable in the literature, but perhaps up to 30% continue to experience some symptoms of psychosis beyond 6 months
    - A couple studies have found rates of 5-7% residual psychosis even 3 years after abstinence
- Studies have NOT found a correlation to predisposing risk factors to account for this subpopulation
    - Makes it more likely to be a direct effect of neurotoxicity from MA

Sato M. A lasting vulnerability to psychosis in patients with previous methamphetamine psychosis. Ann N Y Acad Sci. (1992) 654:160–70.

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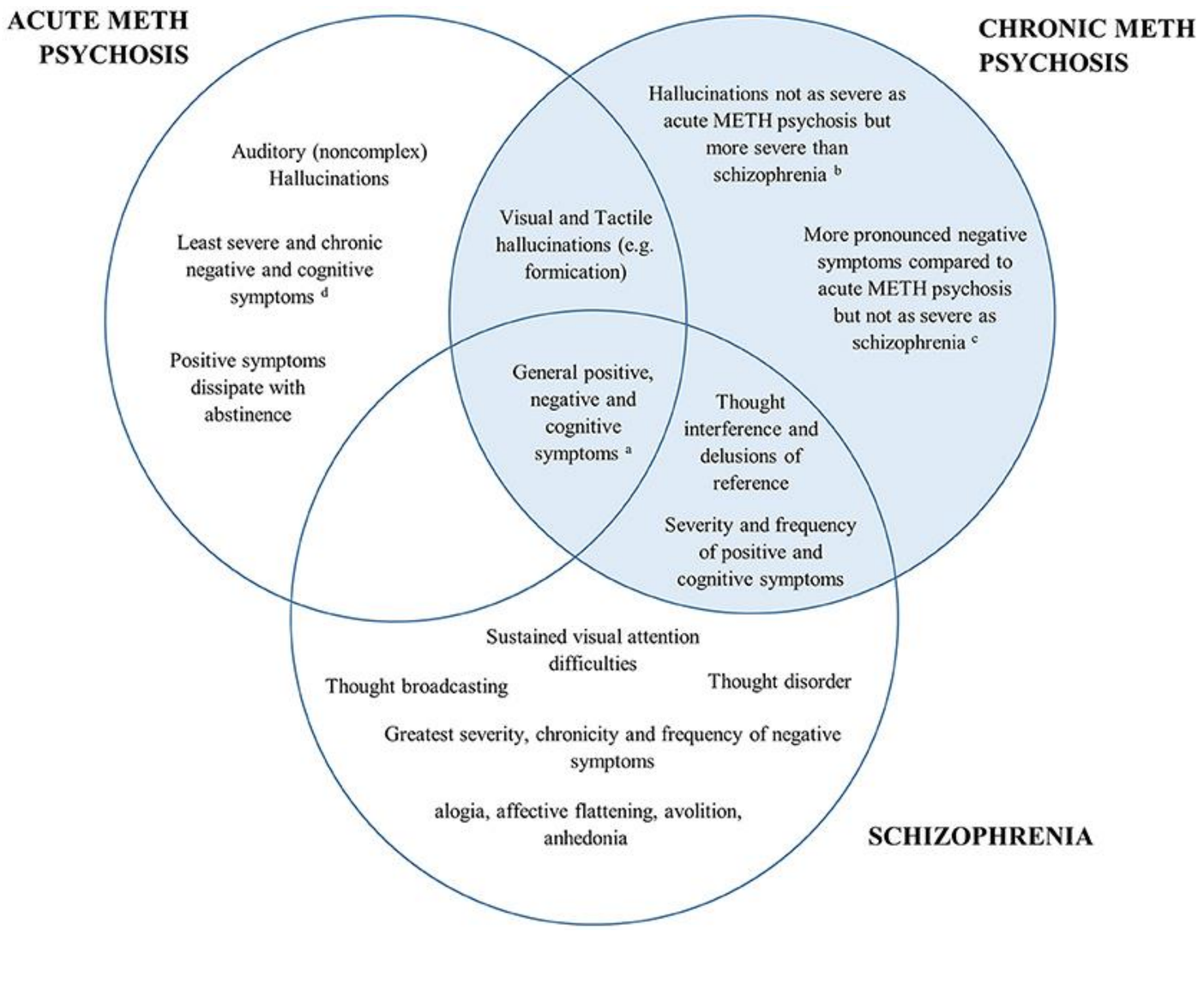

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Treating MA-Induced Psychosis

- Lack of large RCTs to draw guidance
- Majority of cases will be transient, so default stance should be observation and allowance for metabolization
- Acutely, largest concern is safety to self and others. When de-escalatory efforts are not sufficient, medication may be necessary
  - PRN antipsychotics (systematic reviews haven’t found much differences between common choices)
    - But keep 2D6 inhibitory effects in mind…
  - PRN benzodiazepines and/or sleep medication

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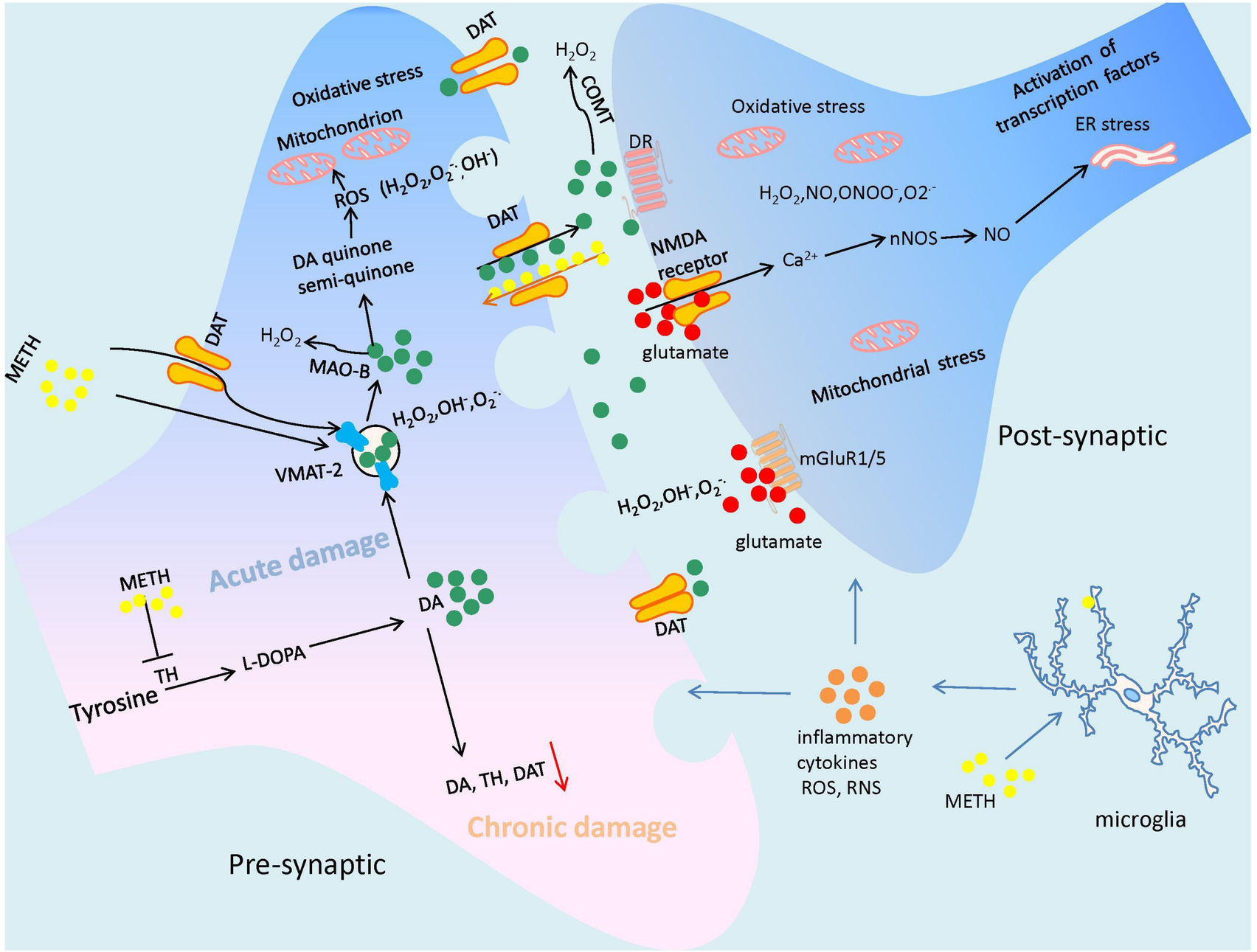
Long-Term Treatment of MA-Induced Psychosis?

- Mainstay: Psychosocial Rehabilitation, Treatment and Recovery
  - Prevention of further use will be most neuroprotective
- No great data to support use of long-term antipsychotics, but also lack of sufficient study
  - Potentially neuroprotective? As well as reduce symptom burden
  - Could LAI (long-acting injectables) be potentially helpful in recovery as well? Anecdotally…
  - Clozapine, amantadine for resistant chronic psychosis?

Ruohollah Seddigh, Amir-Abbas keshavarz-Akhlaghi, Behnam Shariati, "Treating Methamphetamine-Induced Resistant Psychosis with Clozapine", *Case Reports in Psychiatry*, vol. 2014, Article ID 845145, 4 pages, 2014. https://doi.org/10.1155/2014/845145

Gupta M, Gupta N, Esang M, et al. (March 05, 2022) Refractory Methamphetamine-Induced Psychosis: An Emerging Crisis in Rural America and the Role of Amantadine in Therapeutics. Cureus 14(3): e22871. doi:10.7759/cureus.22871



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Methamphetamines and Mania?

- This is only reported as case studies in the literature
- Again, blurred lines of “true mania” vs effect of MA intoxication/withdrawal
  - Stimulant=no sleep
  - Euphoric effect, followed by depressed effect with DA depletion (mirrors mania)
  - Psychosis, as we have seen
- If lasting mania in observed setting without continued MA use (ie, inpatient stay), would suspect underlying bipolar 1 disorder unmasked by MA use
  - High threshold to treat as such though, given overlap of MA use phenotype and additional risks with additional mood stabilizers like lithium and valproic acid

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Take Home Points

- Acute MA-Induced Psychosis has greater chance of visual and tactile hallucinations
- Best acute approach is de-escalation, low-stim, wait out metabolization
- PRNs for safety when necessary, but maybe be mindful of 2D6 inhibition
- Some patients will have residual psychosis for days-weeks, even months-years, with perhaps a small percentage having lifelong chronic MA-induced psychosis
- Psychosocial Rehabilitation, Treatment and Recovery is Gold Standard, not much evidence base to guide medication treatment of chronic psychosis but antipsychotic treatment is reasonable, including LAI
- Methamphetamine-induced “Mania” may be a bit of an overcall, but if sufficient evidence with prolonged course, consider possibility of unmasked BP1 and additional treatment with mood stabilizers