Neuropsychopharmacology open questions

Disclaimer: I haven't received formal education in neuropsychopharmacology. It's a hobby of mine. I read scientific publications, clinical case studies, and attend a few specialized ADHD conferences aimed at psychiatrists, but I don't have direct clinical experience except from my friends.

The goal of this document is two-fold:
– Help me understand pharmacology better by attempting to falsify my hypotheses and questions through the feedback that I will gather.
– Possibly open new areas of research. I haven't found discussions about these topics, so they may be neglected. It's also possible that these were actually discussed but I didn't find the relevant papers.

The claims are not sourced for now because these questions organically came up after reading a lot of scientific papers. For ideas that are the hardest to falsify, I'll add sources so that it makes it easier to prove them wrong.

Time until therapeutic action (SSRIs vs MPH)

Selective serotonin reuptake inhibitors (SSRIs) take 4-8 weeks to start working. The exact mechanisms of action are not well understood. But it's believed that 5-HT1A autoreceptors inhibit VMAT2 exocytosis. These autoreceptors then become desensitized after a few weeks.

Another (less understood) mechanism is the observation that for unclear reasons SSRI administration leads to an increase of the expression of brain-derived neurotrophic factor (BDNF) proteins, which leads to higher tropomyosin receptor kinase B (TrkB) receptors activation. This is thought to lead to an increased hippocampal synaptic plasticity which may play a role in the remission of depressive symptoms.

Methylphenidate is a norepinephrine–dopamine reuptake inhibitor (NDRI). The neurons that it affects also have inhibitory autoreceptors.

1) **Why does methylphenidate work immediately contrary to SSRIs despite that both serotonergic and dopaminergic neurons have autoreceptors that inhibit the recapture of their respective neurotransmitters?**

MAOIs side-effects management

Monoamine oxidase inhibitors (MAOIs) are the antidepressants with the strongest effect size. In particular, nonselective irreversible MAOIs such as Tranylcypromine and Phenelzine successfully treat hopeless patients who don't respond to any of the other medications.

It's probably due to the fact that they are the only drugs that actually increase the global concentration of serotonin in the brain. People with overactive MAOs may not benefit at all from reuptake inhibitors — it may actually worsen their symptoms due to increasing the availability of serotonin in the synaptic cleft. This increased availability may help MAOs break down more serotonin which can deplete the VMAT2s and eventually lower the concentration in the synaptic cleft due to reduced exocytosis. This area is still under research.

Tranylcypromine and Phenelzine were both discovered in 1932. We have considerable clinical experience about their side-effects, pitfalls, and how to successfully treat patients.

Despite their strong efficacy, psychiatrists increasingly stopped prescribing them due to safer (but less effective) antidepressants that were discovered later such as tricyclics and SSRIs/NDRIs. Pharmaceutical companies exaggerated the benefits of these freshly-patented molecules because the expiration of MAOI patents required them to find new sources of income.

The main risk of MAOIs is the life-threatening serotonin toxicity (also known as serotoninergic syndrome). Several pharmaceuticals and street drugs can trigger this syndrome when they are concomitantly taken with MAOIs. In particular: MDMA, SSRIs, tricyclics with reuptake inhibition properties, some opioids but not all (meperidine, methadone, etc.)

The second risk is hypertensive crises. When certain foods are eaten (fermented food, tofu, and others), tyramine can get to unsafe levels as it's not efficiently broken down by MAOs anymore. This increased level of tyramine leads to a high release of noradrenaline in the peripheral nervous system (PNS). This can in turn lead to hypertensive crises. This risk is overblown though — most hypertensive crises can be

solved by waiting a few hours at home. Selective MAO-A inhibitors have a lower risk but are significantly less effective.

These risks make psychiatrists unreasonably scared to prescribe them. In turn this reduces demand which is why there is such a big shortage of MAOIs today.

2) Why hasn't anybody seriously tried to combine MAOIs with drugs that would prevent these side-effects from happening?

- **Competitive SERT blockers** at the sites where SSRIs and MDMA bind could prevent the reuptake inhibition properties of these molecules.
- **Potassium channel blockers** could prevent MDMA's reverse transporting effects.
- **Competitive weak agonists of α1 adrenergic receptors** with high Ki values may prevent hypertensive crises by preventing the excessive binding of noradrenaline due to increased tyrosine concentration.
    - **TODO**: read about the parts of the brain that bypass the BBB and potential implications of α1 agonism in those

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Reducing time until therapeutic action for SSRIs

Exocytosis-promoting molecules

SSRIs are safe drugs for treating depression. Although their average effect size is not very high, they are popular as a first-line treatment option.

Their main downside is that it takes 4-8 weeks before knowing whether they work or not. For patients with suicidal ideation, this timeframe is often unreasonable.

The exact reasons why they take so much time to start working are not entirely understood. The main theory is that 5-HT1A autoreceptors inhibit exocytose but get desensitized after a few weeks. The other popular theory is related to the increased expression of brain-derived neurotrophic factor (BDNF) proteins, but this is irrelevant to this question.

MDMA is a potent molecule promoting the exocytose of serotonin in the synaptic cleft. While initially synthetized by Merck — a pharmaceutical company — it's now only used as an illegal party drug. When used at very high dosages, it can use serotoninergic syndrome.

SSRIs dampen the effect of MDMA by preventing it from entering the presynaptic neurons through SERT. Studies show that — contrary to popular belief — SSRIs are actually protective against MDMA-induced serotonin toxicity. This fact combined with low prescribed doses may make MDMA a very safe drug — although this requires further research to (dis)prove that.

MDMA has the property of unconditionally causing the exocytosis of serotonin, preventing 5-HT1A autoreceptors from having an effective inhibitory action. It is believed that the increased concentration of serotonin in the synaptic cleft eventually leads to the desensitization of the autoreceptors. MDMA could then be safely stopped.

3) Why don't we prescribe exocytosis-promoting molecules such as MDMA when initiating SSRI treatments?

Autoreceptor antagonists

Similarly, preventing autoreceptors from having an inhibitory action would likely help reduce the time it takes for SSRIs to start working. There are some studies around pindolol — a non-selective ß-blocker with autoreceptor antagonist properties — with preliminary evidence that suggests that it effectively reduces the time before SSRIs start working by around 2-3 weeks. Further research is needed to confirm those results.

4) Why don't we prescribe autoreceptor antagonists such as pindolol when initiating treatment to make patients respond faster to the treatment and augment SSRIs?