Antidepressants and 3,4-methylenedioxymethamphetamine (MDMA): Blunted Experiences & Mechanisms of Drug Interaction

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BACKGROUND

• It is hypothesized that dysregulated monoamine (serotonin (5HT), norepinephrine (NE), dopamine (DA)) neurotransmission contributes to the development of depression, anxiety, and posttraumatic stress disorder (PTSD).

• Conventional first-line pharmacologic treatment options for these disorders such as antidepressants target 5HT, NE, or DA neurotransmission via inhibition of the pre-synaptic reuptake (carrier) pump.

• MDMA has a complex mechanism of action, although it utilizes the presynaptic reuptake pump for carrier mediated release of 5HT, NE, and DA.

• In recent years, MDMA-assisted psychotherapy has built a promising evidence base in the treatment of PTSD and recently been fast-tracked by the US Food and Drug Administration (FDA) due to its potential as a break through therapy for phase III trials.

• As psychedelic science progresses, psychedelics and antidepressants may formally assume competitive positions in the healthcare marketplace.

• Likely, in the near future, knowledge on how to manage transitioning from conventional antidepressant treatment to MDMA-assisted psychotherapy and vice versa will be clinically important for optimal safety and efficacy.

OBJECTIVE

• Summarize what is known about drug interactions between first-line antidepressants and 3,4-methylenedioxymethamphetamine (MDMA).

METHODS

• A literature review of articles indexed in MEDLINE was conducted using search terms 'MDMA and (antidepressant or SSRI or SNRI or bupropion or mitrazapine)'.

• No formal inclusion or exclusion criteria was utilized, however only human studies were reviewed in detail.

• References of reviewed articles were further searched for pertinent articles and information.

• Anecdotal evidence from sources such as Erowid, Bluelight Forum, Drugs-Forum, and Reddit were used to supplement, provide context, and verify information gathered from scientific sources.

FINDINGS

MDMA and Antidepressants: Human Studies on Drug Interaction

<table>
<thead>
<tr>
<th>Study</th>
<th>Antidepressant Agent</th>
<th>Antidepressant Class</th>
<th>MDMA subjective effect</th>
<th>MDMA physical effect</th>
<th>MDMA concentration in blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Fluoxetine (Prozac)</td>
<td>SSRI</td>
<td>↓ BP</td>
<td>↑ 15%</td>
<td>Not described</td>
</tr>
<tr>
<td>3, 4</td>
<td>Paroxetine (Paxil)</td>
<td>SSRI</td>
<td>↓ BP, ↓ HR, ↓ PD, ↓ T</td>
<td>↑ 30%</td>
<td>Not described</td>
</tr>
<tr>
<td>5</td>
<td>Citalopram (Celexa)</td>
<td>SSRI</td>
<td>↓ BP</td>
<td>↑ 16%</td>
<td>Not described</td>
</tr>
<tr>
<td>6</td>
<td>Duloxetine (Cymbalta)</td>
<td>SNRI</td>
<td>↓ BP, ↓ HR, ↓ T</td>
<td>↑ 15%</td>
<td>Not described</td>
</tr>
<tr>
<td>7</td>
<td>Wellbutrin (Buproprion)</td>
<td>DNRI</td>
<td>↑ duration</td>
<td>↑ HR</td>
<td>Not described</td>
</tr>
</tbody>
</table>

MDMA and Antidepressants: Pharmacokinetics

<table>
<thead>
<tr>
<th>Pharmacokinetic Interaction With Antidepressants</th>
<th>DMMA</th>
<th>Antidepressant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blocks serotonin, norepinephrine, and dopamine reuptake pumps</td>
<td>1. Agent specific: Blocks serotonin, norepinephrine, or dopamine reuptake pumps (SSRI, SNRI, DNRI)</td>
<td></td>
</tr>
<tr>
<td>Binds with SHT2A receptors</td>
<td>2. Synaptic Clift Post synaptic membrane</td>
<td></td>
</tr>
<tr>
<td>Releases serotonin, norepinephrine, and dopamine from vesicles and into synapse via carrier mediated release</td>
<td>3. Neurone A Neurone B</td>
<td></td>
</tr>
</tbody>
</table>

• When an antidepressant binds to the 5HT reuptake pump, MDMA is unable to reach synaptic vesicles and cause carrier-mediated serotonin release, resulting in diminished effects, however binding to the DA reuptake pump doesn’t interfere with the action of MDMA.

DISCUSSION

• Antidepressants that work by blocking the 5HT reuptake pump drastically attenuate psychodelic effects of MDMA.

• Combining antidepressants with MDMA in healthy volunteers did not result in serotonin syndrome or worsened physical toxicity and may be protective against MDMA associated neurotoxicity.

• Antidepressant effect on MDMA response was reversible with a 10-14 day washout period, however studies were conducted in healthy volunteers after 1-5 days of use.

• Differences between healthy volunteers taking antidepressants in the short term and persons with mental illness taking antidepressants in the long term are probable due to long term neuroadaptation events associated with antidepressant efficacy or differences in brain structure.

• In multidisciplinary association of psychedelic studies (MAPS) sponsored trials, subjects were required to taper off their antidepressants prior to trial participation.

CONCLUSIONS

• Antidepressant taper and washout prior to MDMA-assisted psychotherapy is likely required for therapeutic effect.

• The optimal duration of washout is unknown, although 2 weeks is reasonable based on existing data and current clinical trial protocols.

REFERENCES