fortune Journals

Research Article

ARCHIVES OF
CLINICAL AND
BIOMEDICAL RESEARCH

ISSN: 2572-5017

The Consequences of Drug-drug Reactions Impose Limits on Formulating a Cure for Alzheimer's Dementia

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Abstract

This article uses the example of drugs that might cure Alzheimer's dementia in order to illustrate that consequences of undesirable drug-drug interactions may limit the treatment that may be safely used for any medical condition. As many as 18 elements may participate in the cause of AD, and their suppression may require choosing from 24 individual drugs. That number of drugs may be greatly reduced by excluding those that cause undesirable consequences from drug-drug interactions between the two drugs in each pair. Also, there is a limit to the number of drugs that is tolerable, especially in the elderly who have other conditions requiring drugs. In fact, meaningful simplification of therapy intended to cure a problem such as AD, that has several contributing components, can often be achieved only if there are proxies for those components. In that regard, the present article is intended to make the task easier by providing just two proxies, i.e., dopamine (DA), and serotonin (5-HT), for the 24 drugs that might potentially cure AD. Levels of DA and 5-HT are decreased in AD and each of them has critical importance for brain function, so raising their levels stands a good chance to cure AD. After excluding from the 24 drugs, those pairs of drugs that produce undesirable effects from consequences of drug-drug interactions, only nine drugs remain that may be safely used.

Keywords: Alzheimer's dementia; Drugs; Serotonin (5-HT); Dopamine (DA); Brain; Pathogenesis

Background

The need to find potentially effective drug treatment to cure Alzheimer's dementia (AD), requires consideration of three related problems: first, the numerous elements that contribute to the pathogenesis of AD; second, the large number of drugs that are required in order to address and benefit those elements and, therefore, that have the potential to cure the dementia; and third, the possibility for drug-drug interactions and their potential, undesirable consequences. This article addresses the problem by using recommendations made in previously published articles, for the drugs that might be used in an attempt to cure AD, and examining them with regard to possible undesirable consequences of drug-drug interactions.

Introduction

Reviews have shown as many as 18 elements that may contribute to the pathogenesis of AD [1,2], and that addressing those elements may require 24 drugs. There is a limit to the number of drugs that is tolerable to an individual patient; pragmatically, that limit is only one or two pairs, with each pair containing two members chosen from the 24 drugs that, alphabetically, are: aducanumab, amantadine, amitriptyline, aripiprazole, bromocriptine,

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Citation: Jeffrey Fessel. The Consequences of Drug-drug Reactions Impose Limits on Formulating a Cure for Alzheimer's Dementia. Archives of Clinical and Biomedical Research 9 (2025): 222-225.

Received: April 16, 2025
Accepted: April 24, 2025
Published: May 13, 2025

Fessel J., Arch Clin Biomed Res 2025
DOI:10.26502/acbr.50170455

bupropion, buspirone, cabergoline, desipramine, donanemab, dulaglutide, fluoxetine, lecanemab, levodopa, lithium, memantine, phenelzine, pramipexole, quetiapine, rimantadine, ropinirole, roscovitine, rotigotine, venlafaxine. Not only is it difficult to choose which causal elements to treat and with what drug but there may not have been a clinical trial with results that support the choice of drugs [3]. The following analysis short circuits the dilemma of a large list of potentially effective drugs by using two proxies, dopamine and serotonin, because each of those is deficient in the brains of persons with AD, so raising the levels of those two proxies should have a high likelihood of curing the dementia [4,5]. The 24 drugs include 6 that affect neither dopamine nor serotonin (aducanumab, donanemab, dulaglutide, lecanemab, rimantadine, roscovitine), 9 that affect only dopamine (amantadine, bromocriptine, cabergoline, desipramine, levodopa, memantine, pramipexole, ropinirole, rotigotine), 1 that affects only serotonin (buspirone), and 8 that affect both dopamine and serotonin (amitriptyline, aripiprazole, bupropion, fluoxetine, lithium, phenelzine, quetiapine, venlafaxine) for a total of 24 drugs. Removing the six that affect neither DA nor serotonin leaves 18: amantadine, amitriptyline, aripiprazole, bromocriptine, bupropion, buspirone, cabergoline, desipramine, fluoxetine, levodopa, lithium, memantine, phenelzine, pramipexole, quetiapine, ropinirole, rotigotine, and venlafaxine [6,7].

Increasing dopamine and serotonin levels by the above 18 potentially effective drugs may incur serious drug-drug interactions, and only 9 drugs remain after eliminating those whose drug-drug interactions cause serious consequences

Consequences of drug-drug interactions may require a reduction in the number of the above 18 potentially effective drugs [8-10]. Thus, phenelzine may interact with buspirone and amitriptyline to cause hypotension; it also may cause increased serotonin and the *s*erotonin syndrome via interactions with buspirone, amitriptyline, lithium, and dulaglutide (Table 1) [11].

Phenelzine may also interact with amantadine, bromocriptine, cabergoline, pramipexole, ropinirole, or rotigotine, to cause severely increased dopamine and a hypertensive crisis [12-15]. Interaction between the latter six drugs and aripiprazole or quetiapine, may cause a psychosis because of increased dopamine levels via either dopamine agonism or inhibition of dopamine's interaction with its receptor [16]. Increased QT interval in the electrocardiogram and cardiac arrythmia may occur if quetiapine or aripiprazole are used with lithium, valproic acid, or amantadine (Table 2). Lithium toxicity is increased by amantadine, memantine, and GLP agonists. Thus, phenelzine, aripiprazole, quetiapine, and lithium, should be eliminated, leaving 14 drugs: amantadine, amitriptyline, bromocriptine, bupropion, buspirone, cabergoline, desipramine, fluoxetine, levodopa, memantine, pramipexole, ropinirole, rotigotine, and venlafaxine. Consequences of other potential drug-drug interactions are shown in Table 3 [17-18].

Table 1: Drug-drug ineractions with key concerns.

Drug combination	Risk Level	Key Concern
Phenelzine + amitriptyline	⃠ Severe	Serotonin syndrome, hypertensive crisis
Phenelzine + buspirone	⃠ Severe	Serotonin syndrome
Phenelzine +lithium	⚠ Moderate	CNS toxicity
Fluoxetine + buspirone	⚠ Moderate	Serotonin syndrome
Fluoxetine +lithium	⚠ Moderate	Serotonin syndrome, toxicity
SSRI + Amitriptyline	⚠ Moderate	TCA toxicity

Footnotes: MAOI = monoaminoxidase inhibitor, e.g., tranylcypramine, phenelzine. SSRI = selective serotonin reuptake inhibitor, e.g., fluoxetine. SNRI = selective norepinephrine reuptake inhibitor, e.g., venlafaxine. TCA = tricyclic antiderpressant, e.g., amitriptyline.

Table 2: Major Interactions.

1. **Serotonin syndrome risk due to increased serotonin levels:**
o fluoxetine + amitriptyline, bupropion, buspirone, lithium
o buspirone +fluoxetine or amitriptyline
o lithium + fluoxetine, amitriptyline, or buspirone
2. **Lowered seizure threshold:**
o bupropion + amitriptyline, fluoxetine, lithium.
3. Dopamine overload with risk of psychosis:
o levodopa + bromocriptine, cabergoline, pramipexole, ropinirole, rotigotine
4. QT prolongation risk:
o amitriptyline + fluoxetine, bupropion, or buspirone.

Citation: Michael Mouawad, Leena Nabipur, Devendra K. Agrawal. Impact of Antidepressants on Weight Gain: Underlying Mechanisms and Mitigation Strategies. Archives of Clinical and Biomedical Research. 9 (2025): 222-225.

Fessel J., Arch Clin Biomed Res 2025
DOI:10.26502/acbr.50170455

Table 3: Consequences of other potential drug-drug interactions.

Drug Pair	Interaction Risk	Notes
Levodopa + Lithium	⚠ Moderate	Watch for CNS toxicity
Levodopa + Memantine	⚠ Mild to Moderate	Monitor for confusion, hallucinations
Levodopa + Rimantadine	⚠ Mild to Moderate	Potential synergy, monitor for dyskinesia
Lithium + Memantine	⚠ Moderate to Serious	Rare neurotoxicity risk
Lithium + Rimantadine	⚠ Mild	Overlapping CNS side effects

CHAT GPT was asked the following question and gave the following response. Query: 'what drug-drug interactions occur between drugs in pairs when each pair contains two different members taken from the following drugs: amantadine, amitriptyline, bromocriptine, bupropion, buspirone, cabergoline, desipramine, fluoxetine, levodopa, memantine, pramipexole, ropinirole, rotigotine, and venlafaxine?' [19,20]. Response: 'amantadine & amitriptyline: this combination may increase side effects such as dry mouth, constipation, difficulty urinating, confusion, and blurred vision. More severe effects could include hallucinations, seizures, and irregular heart rhythms. Amantadine & bupropion: both drugs lower the seizure threshold, increasing the risk of seizures [21-23]. Fluoxetine & buspirone: this combination may increase the risk of serotonin syndrome, which can cause symptoms like confusion, rapid heart rate, and high blood pressure. Levodopa & bromocriptine: these drugs are both used for Parkinson's disease and may enhance each other's effects, potentially leading to excessive dopamine-related side effects. Venlafaxine & cabergoline: this combination may lead to increased serotonin levels, raising the risk of serotonin syndrome.

That series of responses contains nine drugs from which five (amantadine, bupropion, buspirone, levodopa, capergoline) are semi-arbitrarily chosen for removal, leaving from the 14 drugs listed above, just nine that remain from the original 24 [24,25].

Conclusion and Summary

Recommendations for formulating drugs to treat any particular condition, should ensure that those drugs do not incur unacceptable drug-drug interactions, and should remove those that provoke such interactions. This article used AD for illustrative purposes and showed that unacceptable drug-drug interactions reduced the original list of 24 recommended drugs to just nine. The illustrated principle has general applicability.

Conflicts of interest: There are no conflicts of interest.

Acknowledgements

No funds for this article were received from the private or public domains. There are no conflicts of interest. CHAT GPT was employed to ascertain the drug-drug interactions mentioned in this article.

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Fessel J., Arch Clin Biomed Res 2025
DOI:10.26502/acbr.50170455

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Citation: Michael Mouawad, Leena Nabipur, Devendra K. Agrawal. Impact of Antidepressants on Weight Gain: Underlying Mechanisms and Mitigation Strategies. Archives of Clinical and Biomedical Research. 9 (2025): 222-225.