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***MYTHS AND REALITY ON CAUSES OF  
DRUG-INDUCED DEPRESSION***

*Summarized from:*

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with Depression. Psychiatry. Vol. 5, No. 12. Dec 2008. 28-41*

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Side Effects. Current Psychiatry. April 2008. Vol.7, No. 4. 61-74.*

### **Drugs Associated with Depression**

The US Food and Drug Administration have been very attentive to prescribed drugs being the cause of depression. “Gold Standard” studies focusing on depression caused by prescribed drugs are very slim. In researching the available information on the subject, it was found that there are only a few types of drugs that have a close link with the induction of depression. On the other hand, there are several drugs such as isotretinoin, rimonabant, and alpha interferons, which have the potential for idiosyncratic reactions, which are less likely to be detected in the larger studies. The discovery of this information has led to the suggestions that caution and very careful monitoring are necessary for many drugs, the above mentioned only being a few out of this list.

The FDA has had many concerns about antidepressant drugs leading to suicidal thoughts also, which lead to warnings of drugs involving suicidal thoughts, all within the past two years. Some of these drugs include Chantix and many antiepileptic drugs.<sup>1,2</sup>

The idea of drug-induced depression (DID) is not new to the medical field. Freis reported on mental health depression in association with antihypertensive drugs.<sup>3</sup> Also, an English Scholar, Robert Burton, associated alcohol with melancholy, and if alcohol is considered a drug, then the idea of drug-induced depression can be dated back 1000’s of years.

The main focus here is on drugs that are used in primary care settings and internal medicine and are associated with drug-induced depression. Medications that are associated with psychiatric disorders, such as antipsychotics or anticonvulsants, will not be discussed.

### **Procedural Problems, Causes, and the Evidence**

The detection of drug-induced depression is a major task in determining the cause of depression, which will be based on any evidence linked to the depression. For example, if after taking a medication

for a few months a patient is complaining about feelings of sadness or melancholy, naturally the first instinct would be to think that it is associated with the new medication they recently started taking. However, it is important to investigate whether this person may have had some past issues with depression, which could be linked to the problem they are having now.

There are several helpful ways to determine the causes of any signs or complaints of depression and/or suicidal thoughts in patients. Table 1 is called the Naranjo causality scale and is meant to help physicians to determine the cause of the depression or suicidal thoughts.<sup>4</sup> Another way of assessing the origin of the patients’ depression is clinical studies. However, the type and quality of the clinical studies is important when used in the determination. Previously mentioned is the “gold standard” of evidence, which is considered a randomized, prospective, double-blind, placebo controlled study.<sup>5</sup>

The use of controlled studies is prohibited in the evaluating the side effects of drugs and their causes. The reason behind this is that the association of medication with depression is not synonymous with a causal relation. Due to depression becoming apparent for so many different reasons, a study in the etiology of depression is necessary. Although the associations found will most likely be confirmed in prospective studies, observational epidemiological research, along with health and disability issues, is the best evidence to use. Normally, pharmacoepidemiological research studies are considered to be in the high levels of evidence, while the case series data and single-case reports are considered lower levels of evidence. If there are no controlled, prospective studies for a clinician to reference, then they are advised to use their best judgment to make the determination of causality.

*See Table 1 and 2 on next page*

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**Table 1. Naranjo Causality Scale**

Question	Yes	No	Don't Know
Are there prior conclusion reports on this effect?	1	0	0
Was the adverse effect reported after the drug was prescribed?	2	-1	0
Was there improvement in the ADR after the discontinuation of the drug or an antagonist was administered?	1	0	0
Did the ADR return when the drug was prescribed again?	2	-1	0
Are there other possible causes of the adverse effect (other than the drug)?	-1	2	0
Did the adverse effect reappear when a placebo was given?	-1	1	0
Did blood tests show that the drug was found in the blood in amounts considered to be toxic?	1	0	0
Did the adverse effect become more severe when the dose was increased or less severe when the does was decreased?	1	0	0
Was there a similar reaction to the same or a similar drug in any prior prescriptions?	1	0	0
Was the adverse effect verified by objective evidence?	1	0	0
<b>Scoring: &gt; 9 = definite ADR; 5-8 = probable ADR; 1-4 = possible ADR, 0 = doubtful ADR</b>			
<b>KEY: ADR = adverse drug reaction</b>			

**Table 2. Consult Patient's Medication List if Signs of New Psychiatric Symptoms**

Symptom	Documented as a possible cause
<b>Psychosis/Agitation</b>	Anabolic androgenic steroids, antihistmaines, clonidine, corticosteroids, decongestants, didanosine, ethionamide, H2 blockers, isoniazid, nitrates, NSAIDs, opioids, proton pump inhibitors, quinolones, salbutamol, skeletal muscle relaxants, sulfonamides/ trimethoprim
<b>Anxiety</b>	Acyclovir, anabolic androgenic steroids, clonidine, corticosteroids, cyclosporine, decongestants, didanosine, serotonin 5-HT <sub>1</sub> agonists such as sumatriptan, foscarnet, ganciclovir, nitrates, ondansetron, penicillins, skeletal muscle relaxants
<b>Depression</b>	Anabolic androgenic steroids, beta blockers, chloramphenicol, clonidine, corticosteroids, didanosone, digoxin, efavirenz, foscarnet, GnRH agonists, H2 blockers, interferons, isoniazid, isotretinoin, NSAIDs, quinolones, statins, tetracyclines
<b>Delirium</b>	ACE inhibitors, anabolic androgenic steroids, antibiotics (most), anticholinergics, beta blockers, centrally acting antihyperintensives such as methyl dopa and reserpine, cimetidine, clonidine, corticosteroids, didanosine, digoxin, H2 blockers, lidocaine, naltrexone, nitrates, NSAIDs, opioids
<b>Insomnia</b>	Aminophylline, anabolic androgenic steroids, clonidine, corticosteroids, decongestants, didanosine, opioid antagonists, proton pump inhibitors, quinolone antibiotics, salbutamol, skeletal muscle relaxants, tetracyclines

NSAIDs: nonsteroidal anti-inflammatory drugs; ACE: angiotensin-converting enzyme; GnRH: gonadotropin-releasing hormone  
 Source: Prepared for Current Psychiatry by Drs. Sidhu and Balon from references cited in this article

**Table 3. Possible Mechanisms of Drug-Induced Depression**

Drug or Drug Class	Possible Mechanism for DID
Nifedipine, other calcium channel blockers	Block slow influx of calcium into the cell, inhibiting calcium-dependent neurotransmitter release and reducing neurotransmitter amplification through the second-messenger system
Benzodiazepines	Based on rodent studies: decreased release of serotonin in hippocampus (except with alprazolam)
Exogenous corticosteroids	Based on rodent development studies: dexamethasone administration leads to deficits in the number and size of neural cells; reduced function of G-protein-coupled catecholaminergic or cholinergic receptors
Varenicline	Displaces nicotine from acetylcholine receptors, produces low-to-moderate levels of dopamine release, and stimulates mesolimbic dopamine system. May upset the balance in cholinergic-adrenergic tone potentially leading to depression or mania.

### Alleged Pathophysiology of Drug-Induced Depression

Assuming that all drugs produce depression is incorrect, even though there is an excess amount of drugs that are associated with drug-induced depression. A very good example of this problem is the drug, reserpine, which may be the first depressogenic drug to be addressed in a medical journal report.<sup>3</sup> At the time, it was reasonable to associate reserpine with drug-induced depression due to its reduction of biogenic amines. However, this has been criticized recently, with arguments that reserpine is not depressogenic and that the reason behind these accusations lie in the myth of the monoamine hypothesis.<sup>6</sup>

The depletion of biogenic amines continues to be considered a mechanism associated with drug-induced depression, along with many others, which can be seen in Table 2.

### Where to Find Evidence for Drugs and Drug-Induced Depression

Table 4 contains a list of thirteen classes of

medications that allegedly have depressive properties. The majority of this evidence is taken from case reports; however some is available from large-scale trials in which depression was evaluated. You can find more in depth information on the drug classes and their depressive effects in the paragraphs that follow table 3.

#### *Antihypertensives*

##### **Beta Blockers**

Beta blockers may be one of the most recognized, but controversial claims when considering drug-induced depression. It is well-known for its ability to reduce mortality in patients with hypertension, but some concern arose on the underutilization of this drug due to its' side effects and tolerability.<sup>7</sup> The earliest association of beta blockers with drug-induced depression is traced back to 1967 in a letter to the editor of the British Medical Journal.<sup>8</sup> Since this report, many other reports and trials have been made to investigate depression as a side effect of many beta blockers. Even though there were a large number of studies conducted, another study

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**Table 4. Evidence for Drug Induced Depression Associated with Drug Classes**

Drug Class/ Drug	Level of Evidence	Available Literature	Comments	References
Beta Blockers	+/-	Case reports, RCTs, large scale meta-analyses	Evidence is conflicting – propranolol may have the strongest association with symptoms after starting or increasing dose	13, 16, 30-41
Calcium channel blockers	+/-	Case reports, case series, prescription symmetry analysis, cohort study examining suicide rates	Results are conflicting – newer agents have fewer reports.	42-48
ACE inhibitors	+/-	Prescription symmetry analysis	Some reports have found antidepressant effects	46, 49-51
ARBs	+/-	Case reports	Preliminary data suggest some ARBs may have antidepressant effects	52, 53
Antiobesity drugs: rimonabant, taranabant	++	Case reports/ meta-analyses	Neither agent approved in U.S. Taranabant is no longer being developed due to psychiatric side effects.	54-56
Alpha interferons	++	Uncontrolled and controlled studies	No comment	57-61
Beta interferons	---	4 RCTs and one naturalistic study	No comment	62-67
Finasteride	+	Case series, prospective noncontrolled trial	Evidence of DID only exists for men treated for alopecia; no evidence for BPH, but caution warranted, given high doses	69, 70
Isotretinoin	+++	Over 400 case reports, prescription symmetry analysis, case-crossover study	No comment	71-74
Progestrone inserts (Norplant)	+	Case reports, case series, large trials	Large trials suggest that women with higher baseline depressive scores may be at risk as well as women with relationship dissatisfaction	75-81
Leukotriene antagonists	+/-	Collection of single case reports; 3 double-blind RCTs	Conflicting data – cases suggest association; recent analysis of 3 RCTs found no association	82-84
Corticosteroids	+	Case control study, cross-sectional analysis	Results of trials are suggestive of DID, especially in patients aged >65, but not convulsive	85-88
Varenicline	+	Case reports, case series	Enhanced FDA warnings – banned by the FAA; increased anxiety reported in 1 placebo RCT	89-91, 92

Reflects the authors' global assessment of evidence; --- little or no convincing evidence; +/- limited evidence; + moderately strong evidence; ++ strong evidence; +++ very strong/unequivocal evidence

ACE = angiotensin-converting enzyme; ARBs = angiotensin II blockers; BPH = benign prostatic hyperplasia; DID = drug induced depression; FAA = Federal Aviation Administration; FDA = US Food and Drug Administration; RCT = randomized, controlled trial

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done did not support these accusations. This study assessed over 10,500 patients, and concluded that the overall incidence of depression was comparable to the placebo (20.1% vs. 20.5%). According to some large-scale, controlled, and statistically analyzed studies, the connection made between beta blockers and drug-induced depression is not as strong as once believed.<sup>9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19</sup>

When comparing selective and non-selective beta blockers, non-selective beta blockers use a wider variety of extracardiac symptom, but there is not enough evidence from studies showing that beta selectivity has a greater risk of drug-induced depression. Based on the controversial data, it is thought that the original report from 1967 did not consider all of the beta blocker class.

### **Calcium Channel Blockers (CCBs)**

Very similar to beta blockers, calcium channel blockers are very beneficial to certain parts of the population. There are a small amount of studies that were very well put together show that CCBs are associated with drug-induced depression. However, there are two separate case series that implicate that nifedipine is directly associated with drug-induced depression.<sup>20, 21</sup>

A 1996 epidemiologic study, conducted by Hallas, examined several different cardiovascular medications for their association with depression. The study assessed over 11,000 patients on many different cardiovascular medications and antidepressants, evaluated over a pre-determined period of time. The only cardiovascular medications that showed an effect associated with depression are CCB and angiotensin-converting enzyme inhibitors. A following study done on the rate of suicides related to cardiovascular medications showed that ACE inhibitors were the only class of drugs to have a direct relationship to an increased chance of suicide. In this same study, after adjustments were made to the rates of use among the classes, CCBs were also found to have a significant positive association with

increased suicides.

Another investigation held by Dunn, contradicted all the above evidence, finding no direct correlation to drug-induced depression for patients taking the medications, diltiazem and nicardipine.<sup>23</sup> The main reason that this study holds more validity is that it screened for depression in patients based on the assessments of general practitioners' diagnoses over a five year period.

To summarize, considering the difference in methodology and the contradicting results, the evidence linking a CCB as a drug-induced medication is partial. Even though the recently mentioned studies do not hold much value, some medications are less likely to be used, but there are newer medications available that may not be as directly associated with drug-induced depression.

### **ACE inhibitors**

The Hallas study, that was previously mentioned, found a considerable positive connection between the use of ACE inhibitors and the prescribing of concomitant antidepressants. However, some trials have actually found that ACE inhibitors are effective in treating some cases of major depression. When looking at both of these pieces of evidence the conclusion has been made that there is limited evidence that associates ACE inhibitors with drug-induced depression.

### **Angiotensin II blockers (ARBs)**

Two ARBs, valsartan and losartan, are prescribed to patients who have a hard time tolerating or are resistant to the therapy provided with ACE inhibitors. It was discovered that ARBs have a weak connection to drug-induced depression, just as ACE inhibitors. Even though there is a weak link between ARBs and drug-induced depression, there was a study conducted on mice that showed a link between an ARB, losartan, and depression (Gard PR). Basically, the association of ARBs and depression is weak due to the fact that there is only one case study that implies any association between

ARBs and drug-induced depression.

### ***Antiobesity Agents***

Rimonabant, a cannabinoid antagonist and antiobesity agent, can be found in many countries, but was not approved by the FDA. In a meta-analysis study, done by Christensen, discovered that patients taking rimonabant are 2.5 times more likely to discontinue therapy due to depression when compared to the placebo patients.<sup>24</sup> The same study was also reviewed by the FDA and they found that 26 percent of the patients were 2 times more likely to have an adverse psychiatric event or suicidal thoughts.<sup>25</sup> There was also another similar medication that was discontinued based on these discoveries and the psychiatric events experienced by patients. In conclusion, the evidence linking cannabinoid antagonists to drug-induced depression appears strong.

### ***Antivirals***

The clinically used interferons are classified as alpha or beta. The beta interferons are used in the treatment of multiple sclerosis, while the alpha interferons are used to treat hepatitis C.

#### **Alpha interferons**

There have been several controlled and uncontrolled investigations linking alpha interferons with depression.<sup>26,27,28,29,30</sup> In a very recent study on alpha interferons showed that 33 percent of patients treated formed new-onset depression after 12 weeks of using the medication.<sup>29</sup> There is a strong link between drug-induced depression and alpha interferons, but it is recommended that there be a screening for depression before and during the alpha therapy.

#### **Beta interferons**

There is one randomized controlled study that suggests depression when taking beta interferons.<sup>34</sup> A naturalized study was conducted that tested antidepressant use with beta interferons and glatiramer, a non-interferon used for multiple sclerosis, which followed depression levels between both groups. There was no significant difference in the two groups.<sup>32,33,34,35</sup> Although the evidence is less

convincing, this study implies that there is not much risk associated with drug-induced depression and beta interferons.

### **Antimicrobial Agents**

Although delirium is the most common psychiatric symptom associated with antibiotic and antiviral agents, they can cause psychiatric side effects by:

- Directly affecting the neuronal functions
- Indirectly entering the brain at a rapid pace and then taking over the compromised blood brain barrier during infection.

#### **Antibiotics**

Penicillin and its analogues are linked to sedation, anxiety and hallucinations. The majority of cephalosporins have been linked to delirium, most of which are in patients who experience low renal function. However, quinolones, like ciprofloxacin and ofloxacin, seldom cause restlessness, irritability, lethargy, tremors, insomnia, mania, depression, psychosis, delirium, and confusion. Clarithromycin has a strong link to delirium and chloramphenicol may cause depression, but is not commonly used.

Isoniazid is a more commonly used antibiotic, if not the most common, and is highly linked with the cause of delirium, mania, psychosis, and depression. Ethionamide is related to sedation, irritability, depression, restlessness, and psychosis. Also, tetracyclines, when prescribed in high dosages, are known to cause depression, insomnia and irritability.

Another antibiotic, sulfonamides have been known to cause delirium when taken alone, and have been linked to psychosis and confusion when paired with trimethoprim.

#### **Dermatologics**

##### **Finasteride**

Finasteride is a medication used in the treatment of benign prostatic hyperplasia (BPH) and androgenic (androgenetic) alopecia. However, depression has only been associated with the treatment of alopecia. In an uncontrolled study done on 128 men, given 1mg of finasteride per day, were tested for depression

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after 2 months of therapy, finasteride was found to increase symptoms of depression. In conclusion, there is strong evidence that finasteride has a direct association with drug-induced depression.

### **Isotretinoin**

Between the years of 1982 and 2000 there have been more than 400 reports of depression and 37 reports of suicide in patients who received the medication isotretinoin.<sup>36,37</sup> Solely based on this information above, we can conclude that the evidence linking isotretinoin and drug-induced depression is very strong.

### **Hormonal (Contraceptives)**

Norplant, a birth-control agent, has had many cases reported in which women that never had signs of depression prior to the medication, developed major depression within 2 months of beginning the medication. After ceasing the medication the symptoms disappeared within a month. In another study, results were contradictory to the above. This study focused on the depressive symptom studies at 6 and 24 months. There 910 women in the study and 138 were lost to follow up while 295 discontinued use. Of the 295 that discontinued use, 4.4% of 295 had done so because of mood changes. The depressive scores for the women that continued the use of Norplant showed lower depressive scores than those who discontinued its use. The authors of this particular study did not document any direct correlation with drug-induced depression and Norplant.

According to these two large trials, it has been concluded that there is a moderately strong association of Norplant with drug-induced depression.<sup>38</sup> It is recommended that physicians screen the patients for depression prior to use of Norplant. Any signs of depression would warrant not prescribing the medication and possibly offering an antidepressant medication or even psychotherapy, if necessary.

### **Respiratory Agents (Leukotrine Inhibitors)**

Leukotrine inhibitors are made up of a class of medications used to treat persistent asthma. There

were several reports on the leukotrine inhibitor montelukast associated with depression along with 43 other case reports that were stored in the world health organizations records. While the number of cases may imply that leukotrine inhibitors had a direct correlation with drug-induced depression, other related therapies along with other seasonal allergies cannot be overlooked.

In a study, held by Holbrook and Harik-Khan, 536 out of 1,356 patients known to suffer from asthma were given montelukast and tested the patients' "quality of life" using different depression scales, such as the Juniper Mini Asthma Quality of Life Questionnaire. Based in these studies, the authors found no direct connection between montelukast and emotional instability.

In conclusion, it was found that the evidence that may link leukotrine inhibitor to drug-induced depression is limited and would need further research to associate or disassociate it with drug-induced depression.

### **Corticosteroids**

It was unexpected that the research conducted to link corticosteroids to drug-induced depression was very limited and weak. The reason for this is because there have always been well-known polymorphous psychiatric complications associated with these types of drugs, such as euphoria, depression, agitation, irritability, and psychosis. Although these side effects were known and depression was apparent in patients treated with corticosteroids, the main question to be answered was whether the medication was a direct cause of the depression.

There were two studies held that resulted in a relationship between corticosteroids and drug-induced depression.<sup>39,40</sup> The studies both assessed 40 inpatients, 20 who were given corticosteroids and 20 who were not, and the patients were allowed to self-report their depression. Although the presence of depression was greater in those who took corticosteroids, the small group and the use of self reporting gave limitations to the study. The

results of these studies determined that there was no danger of diagnosing a depressive disorder by using corticosteroids, even if depression was a common side effect of the medication.

In another study, contradictory results were found based on a larger sample of patients and the use of the Geriatric Depression Scale to determine the presence of depressive symptoms. The sample was split into two groups after determining whether or not they had signs of depression. While all patients were taking corticosteroids, one group did not have depression while the other did have signs of depression. The results showed that the prescribing of corticosteroids had a strong connection to depressive symptoms, where the connection was even stronger in patients over the age of 65.<sup>41</sup>

In conclusion, based on the above studies, it was determined that there is only a moderately strong association between drug-induced depression and corticosteroids.

### ***Anabolic Androgenic Steroids (AAS)***

Anabolic androgenic steroids have a limited medical benefit. They are frequently used by athletes or bodybuilders to increase size and muscle mass, so that they can gain a competitive edge over other athletes. There are many problems associated with anabolic androgenic steroids, to include: acute paranoia, delirium, mania or hypomania, homicidal rage, aggression, extreme mood swings, increased libido, irritability, agitation and anger.

In a study held with 320 athletes and amateur bodybuilders, anabolic androgenic steroids caused many psychiatric side effects, which became worse as anabolic androgenic steroid use was increased. Another 2-week, double-blind, fixed-order, placebo-controlled, crossover study of healthy male inpatient volunteers, AAS had two main side effects:

- mood elevating effects - increased energy, and increased sexual arousal and drive
- mood-dysphoric effects – irritability, mood swings, increasingly violent feelings, increased

hostility, and cognitive impairments.

Anabolic androgenic steroids, the same as corticosteroids, cause psychiatric symptoms to become worse as the intake amount increases. Normally, the symptoms fade away after a few weeks using the correct antipsychotic medication, but can last up to one month even with medication.

Hormone – Gonadotropin-releasing hormone (GnRH) agonists

Examples of this hormone are leuprolide and nafarelin, which are approved for treating endometriosis, advanced prostate cancer, precocious puberty, and uterine leiomyomata. However, there are some case reports that link these hormones to depression.

### ***Smoking Cessation Agents (Varenicline)***

A smoking cessation agent called varenicline, also known as chantix, had many reports of suicidal thoughts and behavior that had a tendency to develop days to weeks after the start of the medication. A recent report described a patient that already had depression, developing more severe depression. Based on this particular study, it would be too early to decide that depressive symptoms will always occur within the first few weeks of therapy.<sup>42</sup>

Another study, conducted by Tsai, compared patients using varenicline with a placebo group and found that anxiety and irregular or vivid dreams were very common in the varenicline group, which was based on self reporting by the patient.<sup>42</sup>

In conclusion, based on these studies and FDA warnings, physicians should be wary of allowing patients with prior depressive signs to take this medication, as the side effects are very risky. The association of drug-induced depression and varenicline has been found to be moderately strong based in the above evidence. Over-the-Counter and

### ***Other Medications***

Although it may seem unusual, there are many commonly used over-the-counter medications that are linked to psychiatric symptoms. Most commonly used are the cold and allergy medications, reflux

agents and analgesics.

### *Cold Medications*

By pairing the use of antihistamines and decongestants, like phenylpropanolamine, azatadine, loratadine, ephedrine, phenylephrine, pseudoephedrine, and naphazoline can cause atropine-like psychosis that is normally shown in the form of confusion, disorientation, agitation, hallucinations, and memory problems. When decongestants are combined with monoamine oxidase inhibitors (MAOIs), it can cause a very high level of norepinephrine. For this reason, decongestants are prohibited in patients taking MAOIs. Another common medication, ephedrine, is known to cause restlessness, dysphoria, irritability, anxiety, and insomnia.

### *Reflux Medications*

Two of the main classes of reflux medications are proton pump inhibitors, such as omeprazole, and lansoprazole, and H2 receptor antagonists, such as famotidine, nizatidine, and ranitidine. Though these are normally considered to have a harmless side effect, there have been many cases reported of serious neuropsychiatric symptoms, such as mental confusion, agitation, depression, and hallucinations. This is most common in elderly geriatric patients with a low renal function.

The side effects due to H2 receptor antagonists can show up at different times during treatment, depending on the medication. Depression may occur 4-8 weeks after starting treatment of Ranitidine. There have been reports of adverse effects after 2-3 weeks, delirium within 24-48 hours and even sexual dysfunction when taking cimetidine.

Side effects associated with these medications will go away after a few days of ceasing the medication, but ranitidine or cimetidine can cause withdrawal syndrome when stopped immediately, causing anxiety, insomnia, and irritability. Cimetidine also has reported cases of increasing the blood levels and action of tricyclic antidepressants, which can become toxic, which can then cause

tachycardia and other adverse effects.

### *Other Medications*

Ondansetron is a 5-hydroxytryptamine subclass 3 (5-HT<sub>3</sub>) antagonist used for antiemetic therapy and has been strongly associated with anxiety.

Isotretinoin is a retinoid used for very severe cases of acne and can cause very bad cases of depression and suicidal behavior.

Aminophylline and salbutamol are two other medications that are linked to agitation, insomnia, euphoria, and delirium. There have also been many cases reported that methotrexate can cause personality changes, irritability and delirium.

### **Conclusion**

The findings explained in this article should be considered temporary. To review, isotretinoin, rimonabant, and alpha interferons have been found to have the highest risk of drug-induced depression with the medications discussed. Corticosteroids, varenicline, progesterone inserts and finasteride were found to have a moderately high risk of drug-induced depression. Considering that all these agents have valid medical warnings, physicians should compare the disadvantages as well as the advantages of each drug very carefully and on an individual basis.

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