Original article

Treating psychiatric symptoms and disorders with non-psychotropic medications

Vincent Hede, MD; Cédric Devillé, MD

A few drugs prescribed in internal medicine, ie, non-psychotropic drugs, can be used to treat certain neuropsychiatric disorders. For most of these situations, the level of evidence remains low. But when sufficient data becomes available, these molecules are then included in official guidelines for the treatment of neuropsychiatric disorders. In this article we review interesting drugs which may be relevant from an evidence-based medicine point of view, and could become part of psychiatric practice in the future.

Dialogues Clin Neurosci. 2019;21(2):193-201. doi:10.31887/DCNS.2019.21.2/vhede

Keywords: non-psychotropic medication; psychiatric disorder; psychopharmacology; evidence-based medicine

Introduction

Psychotropic medications (PMs) are, according to a formal definition, drugs that affect mental and psychological functions. Many non-psychotropic medications (non-PMs) prescribed for physical (ie, non-psychiatric) diseases also influence brain function, and this influence can be beneficial. In this review, we label as non-PM all drugs for which the main indication does not belong to the field of psychiatry. Here, we discuss several non-PMs that are or might be useful in psychiatry, by improving a psychiatric disorder or symptom in the absence of any physical disease. These benefits have either been known for decades or they are new observations, as with statins. These situations share a common point which concerns the confirmation and validation of non-PM use in psychiatry; this path toward evidence-based medicine is sometimes tortuous.

The study of these molecules has several advantages. First, it provides alternative drugs, which can be scarce in psychiatry. They can be alternatives with fewer side effects in disorders for which there already exist treatments, or alternatives for disorders for which there are no sufficiently efficacious drugs, such as in Alzheimer disease (AD), or autism spectrum disorder (ASD). Second, these molecules have been used for a long time, and there is consequent knowledge about the tolerance and risk profile. Third, it provides potential new drug indications with minimal development cost. Fourth, using non-PMs to treat psychiatric disorders necessarily leads to questioning their mechanisms of action and, in so doing, lead to a better understanding of the pathophysiology of psychiatric disorders.

Non-psychotropic medications and psychiatric disorders

Several non-PMs influence the course of a psychiatric disorder in patients who do not suffer from the physical diseases for which these non-PMs are indicated. Drugs like β-blockers are known for their effect against anxiety, while

Author affiliations: Liaison Psychiatry Unit (Vincent Hede); Young Adult Psychiatry Unit (Cédric Devillé); Department of Psychiatry, Geneva University Hospitals, Geneva, Switzerland. **Address for correspondence:** Dr Vincent Hede, Hôpitaux Universitaires de Genève, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland. (e-mail: Vincent.Hede@hcuge.ch)

others, like antibiotics (such as minocycline), are recent additions to the psychiatric field. In the list below, we focus on several molecules for which there is some evidence of efficacy (the development of non-PMs for neuropsychiatric clinical indications has the advantage for the pharmaceutical industry of a less costly drug development process). Some examples below might be new to some readers, while other non-PMs have been known to be prescribed in psychiatry for decades.

Acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs

There is evidence for a role of inflammation, oxidative and nitrosative stress, and mitochondrial dysfunction in disorders such as depression, schizophrenia, bipolar disorder, and AD.[1] Acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs) protect against oxidative damage, and have shown beneficial effects on mood disorders.[2,3] A moderate antidepressant effect was observed for adjuvant NSAIDs compared with conventional therapy alone in the treatment of bipolar depression.[4] A systematic review and meta-analysis of randomized clinical trials (RCTs) suggests that NSAIDs, in particular celecoxib, decrease depressive symptoms without increased risks of adverse effects.[5] Further trials are needed before making recommendations about the clinical use of anti-inflammatory drugs in the treatment of mood disorders.[6] Very preliminary clinical work also suggests some efficacy of acetylsalicylic acid in schizophrenia.[7]

There is sufficient evidence for some non-psychotropic medications to be recommended in psychiatric guidelines

Epidemiological data show that patients who take NSAIDs long-term are at lower risk of AD, and NSAIDs have generated enthusiasm for reducing the risk of AD.[8] However, clinical trials to date have shown no superiority over placebo for sulindac, piroxicam, acetaminophen, naproxen, nabumetone, ketoprofen, diclofenac, or acetylsalicylic acid.[9] The prescription of NSAIDs cannot be recommended for either prevention or treatment of AD.

Bumetanide

The diuretic bumetanide decreases intraneuronal chloride concentration and thereby facilitates γ-aminobutyric acid (GABA) inhibition. In animal models of ASD, bumetanide restores intraneuronal chloride levels, enhances GABAergic inhibition, and attenuates behavioral symptoms. In a phase II trial, bumetanide reduced the severity of ASD in children and adolescents.[10] A case report suggests that long-term treatment reduced hallucinations and that this treatment may also be useful to treat schizophrenia.[11] However, this was not confirmed in a later small double-blind study.[12]

Clonidine and other α-blockers

The antihypertensive clonidine is a central α-2 agonist that also acts through imidazoline receptors.[13] Guanfacine has the same mode of action, but with less sedation. Both were approved as antihypertensives by the Food and Drug Administration (FDA) in 1974 and 1986. In 2010, they were registered for the treatment of attention-deficit hyperactivity disorder (ADHD) in a pediatric population (6 to 17 years). Both are listed in ADHD treatment guidelines.[14] They are also efficacious in opiate withdrawal, alcohol withdrawal, and smoking cessation, and have been studied in Tourette syndrome, with benefits on behavior and tics.[15] Clonidine is effective in smoking cessation.[16] It could also reduce traumatic memories and nightmares in patients with post-traumatic stress disorder (PTSD). A systematic review found slight but positive evidence for prazosin, an α-1 blocker, for the treatment of nightmares in PTSD.[17]

Gabapentin and other anticonvulsants

The antiepileptics valproic acid, lamotrigine, and carbamazepine have a recognized role in psychiatry that will not be commented on here. Gabapentin inhibits the α2δ subunit of voltage-dependent calcium channels. It is indicated for neuralgias, restless leg syndrome, and partial seizures. It has shown efficacy in alcohol craving, alcohol withdrawal, and several anxiety disorders including social anxiety.[18] Its close compound pregabalin has been registered in the United States for use in social anxiety, fibromyalgia, and generalized anxiety.

Hydroxyzine and other antihistamines

The first antihistamines used against allergic conditions are antagonists to the histamine H1 receptor, which have also long been prescribed as sleeping pills; diphenhydramine and several other antihistamines have been registered in

many countries as over the counter (OTC) sleeping pills.[19] Hydroxyzine was registered by the FDA a long time ago, in 1956, for the symptomatic relief of anxiety; the results are considered equivalent to those of other anxiolytics such as benzodiazepines in terms of efficacy, acceptability, and tolerability, but this indication is recommended by only a few authors.[20] Hydroxyzine, like other early antihistamines, has anticholinergic and antidopaminergic effects that participate in the side effect profile. The more recent H1-blockers such as cetirizine or loratadine have not been studied as sleeping pills, although cetirizine induces some sedation. Pitolisant, an antagonist to the H3 receptor, has been registered in several countries to treat narcolepsy. The H3 receptors being presynaptic, their blockade leads to more histamine and other neurotransmitters being released, and pitolisant and other H3 antagonists are being studied as nootropic agents.

Ketamine and other glutamatergic antagonists

Ketamine is a nonselective NMDA glutamatergic receptor antagonist. While GABA serves as the main site-to-site (ie, with rather short axons) inhibitory transmitter, glutamate is the main excitatory site-to-site one, with too much glutamate release leading to neurotoxicity. Ketamine is used in anesthesia and for the management of post-surgery pain. Several randomized controlled trials (RCTs) of intravenous ketamine provide findings of efficacy in treatment-resistant depression, bipolar depression, and suicidal ideation.[21] Intranasal esketamine, the S enantiomer of ketamine, was accepted in early 2019 by the FDA for treatment-resistant depression.[22] Amantadine, a weak NMDA receptor antagonist with antiviral properties, can play a role alone or in association with cholinesterase inhibitors to enhance cognitive function and reduce behavioral symptoms in AD.[23]

Minocycline and other antibiotics

Minocycline is a tetracycline bacteriostatic antibiotic. Apart from its antibacterial properties, minocycline has anti-inflammatory, antiapoptotic, and neuroprotective effects.[24] Minocycline might be useful in major depressive disorder (MDD) and in bipolar depression.[25-27] A link between high level of Il-6 or brain glutathione and a better response to minocycline is supposed. The clinical effects of adjunctive minocycline on the negative symptoms of schizophrenia are controversial,[28,29] although a recent meta-analysis shows positive results.[30]

Rifampicin inhibits bacterial RNA polymerase. It inhibits the formation of amyloid-β, tau protein and α-synuclein, with promising results in animal models of AD.[31,32] The progression of AD might be slowed with rifampicin associated with doxycycline or rifampicin alone.[33,34] These results were not confirmed in other trials, maybe because of dose and length of treatment issues.[35,36]

N-Acetylcysteine and over-the-counter drugs

N-acetylcysteine (NAC) is prescribed for its mucolytic effects and as antidote in cases of acetaminophen overdose by providing a precursor for the glutathione synthetase pathway.[37] The rationale for studying NAC in psychiatry is based on its interference with several signaling pathways that play a role in regulating apoptosis, angiogenesis, cell growth and inflammatory pathways, as well as on its modulatory action on glutamatergic and dopaminergic systems.[38] The efficacy of NAC was discussed in an extensive review which considers an astonishingly long list of psychiatric disorders, with the conclusion that no firm recommendation could be given yet for NAC in any indication.[39] The highest evidence, (at least one prospective high-quality RCT) were found for dependency treatment (cannabis, cocaine, and nicotine), unipolar and bipolar depression, schizophrenia, and trichotillomania. According to a 2018 meta-analysis, adjunctive NAC has efficacy in schizophrenia, but not in mood disorders or major depressive disorder.[40] Further high-quality RCTs are warranted to determine the role of adjunctive NAC in the treatment of major psychiatric disorders.

S-adenosyl-L-methionine (SAMe), sold as a dietary supplement in United States and Canada, is an endogenous, intracellular amino acid metabolite involved in multiple crucial biochemical pathways, including biosynthesis of hormones and neurotransmitters. During the 1970s and 1980s, SAMe was studied after intravenous administration. A review of SAMe in major depression found limited evidence of efficacy to support its use as a monotherapy or as augmentation with other antidepressants; the authors were optimistic, but recognized that studies were of insufficient methodological quality.[41]

Tryptophan and hydroxytryptophan (5-HTP), amino acids that are precursors of serotonin, are sometimes called natural alternatives to traditional antidepressants, but they are less effective and safety concerns have not been clarified.[42]

Pramipexole and other antiparkinsonian drugs
Pramipexole is a dopamine D2 and D3 receptor agonist indicated in Parkinson disease (PD) and restless legs syndrome. Pramipexole is effective in unipolar and bipolar depression in association with antidepressants or mood stabilizers.[43] It has also been studied in monotherapy with results comparable to fluoxetine, but with side effects at high doses.[44] Most data concern its use as augmentation treatment for which low or moderate doses up to 1.5 mg are sufficient with good safety concerns. The rate of manic or hypomanic switch is also very low and pramipexole is quoted as an option for bipolar depression in guidelines.[45] In drug-resistant depression, it is an alternative to other treatments (lithium, aripiprazole, or quetiapine) with easier use and fewer side effects.

Other antiparkinsonian drugs, such as ropinirole, pergolide, and bromocriptine, have been less extensively studied in depression. Very anecdotally, in a small case series dating back 50 years, delusional depression responded to L-dopa, while nowadays delusion would be a contraindication to dopamine agonists.[46]

Propranolol and other β-blockers
These cardiovascular medications reduce sympathetic nervous system activity by blocking β-adrenergic receptors. Lipophilic β-blockers pass the blood-brain barrier, which is the case with propranolol.[47,48] Aside from cardiovascular indications, migraine, and essential tremor, propranolol might be useful in panic attacks.[49] Also, a meta-analysis showed no difference between propranolol and benzodiazepines on anxiety, panic attack frequency, and avoidance behavior, although equivalence was not proven.[50] Several studies showed that propranolol decreased apprehension before diagnostic tests or dental interventions and some clinicians prescribe it to persons in stressing situations, like exams, playing music, or acting, with the benefit of no sedation. Since β-blockers inhibit memory consolidation, propranolol has been studied in PTSD prevention.[51-53] Studies on how soon it should be administered after a trauma are ongoing. A recent RCT concluded that propranolol associated with brief memory reactivation had significant results compared with placebo in the treatment of PTSD.[54]

Statins
Statins, which act as hydroxylmethyl glutaryl coenzyme A reductase inhibitors, have been studied in patients with schizophrenia. A meta-analysis of 6 RCT, totalizing 169 patients using statins as adjunctive therapy, found a significant improvement for negative and positive symptoms.[55] Hypotheses underlying these effects concern anti-inflammatory properties, interactions with P-glycoprotein substrates, or neuroprotective effects through N-methyl-D-aspartate receptor upregulation and increase of muscarinic receptor binding. In a large observational study, a reduction of self-harm has been observed. The authors checked the files of 142 691 patients diagnosed with bipolar disorder, schizophrenia, or nonaffective psychosis, and found a reduction in psychiatric hospitalization rates in patients receiving statins, L-type calcium channel antagonists or biguanides such as metformin.[56]

Thyroid hormones
While there is no evidence that triiodothyronine (T3) alone is a useful antidepressant, it is recommended as adjunctive medication for the treatment of resistant depression.[57,58] Evidence for its efficacy comes mainly from its association with tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs).[59] Using thyroid hormones in bipolar depression is also being discussed, but with less evidence.[60]

Outlook and conclusions

The prescription of non-PMs in psychiatric disorders indicates that the future of psychiatric treatment is not based solely on PMs. When favorable results with a non-PM in a purely psychiatric indication are confirmed, the non-PM, after a period of off-label use, is included in official guidelines *(Table I)* and eventually registered by the FDA or other agencies. Each guideline uses its own evaluation of evidence with less or more requirements. Usually, level 1 evidence corresponds to high-quality meta-analysis, level 2 to high-quality double-blind RCT, level 3 to other studies, and level 4 to expert opinions.

The hormone T3 is recommended as a second-line adjunctive medication in treatment-resistant depression with a level 2 evidence while there already is level 1 evidence for ketamine perfusion which was still considered as experimental in some guidelines for depression.[58] Pramipexole, intravenous ketamine, NAC, and T3 are considered as third-line adjunctive treatment in bipolar depression, with level 3 evidence.[45] It is noteworthy to underline that a low level of evidence, such as a level 3, does not necessarily mean lower

DRUG	DRUG CLASS	OFFICIAL INDICATION	PSYCHIATRIC DISORDER	RECOMMENDATION IN PSYCHIATRY*
5-HTP	Amino acid	None	Depression	
Amantadine	NMDA receptor antagonist	Parkinsonian symptoms, influenza treatment and prophylaxis	Alzheimer disease	
Bumetanide	Loop diuretic	Swelling	Autism spectrum disorders, schizophrenia	
Clonidine	Central α-2 agonist	High blood pressure, cancer pain, ADHD in pediatric population	ADHD Smoking cessation	Recommended in ADHD if no response to other treatments and after advice from tertiary ADHD service[14] Recommended as second-line treatment in smoking cessation[16]
Gabapentine	Agonist GABA	Epilepsy, neuropathic pain	Anxiety disorder, bipolar disorder	Yes as third-line treatment in panic disorder, second-line in social anxiety disorder, and third-line adjunctive therapy in PTSD[62] As first-line treatment in anxiety disorders associated with bipolar disorder[61] In maintenance therapy in bipolar disorder[45]
Guanfacine	Central α-2 agonist	High blood pressure, ADHD in pediatric population	ADHD	Recommended if no response to other treatments and after advice from tertiary ADHD service[14]
Ketamine in perfusion**	NMDA receptor antagonist	Anesthesia	Unipolar and bipolar depression	As third-line adjunctive treatment in bipolar depression[45]
Minocycline	Antibiotics	Infections, acne	Depression	
NAC	Amino acid	Mucous secretions in broncho-pulmonary disorders, antidote for paracetamol overdose	Unipolar and bipolar depression, schizophrenia	As third-line adjunctive treatment in bipolar depression[45]
NSAIDs	Anti-inflammatory	Pain, fever	Mood disorders	
Acetylsalicylic acid		Cardiovascular prophylaxis	Schizophrenia Depression	
Pramipexole	Antiparkinsonian	Parkinsonian symptoms, restless legs syndrome	Unipolar and bipolar depression	As third-line adjunctive treatment in bipolar depression[45]

Table I. Non-psychotropic drugs and their non-psychiatric and psychiatric uses. 5-HTP, L5-hydroxytryptophane; NAC, N-acethyl cysteine; NSAID, Nonsteroidal anti-inflammatory drug; ADHD, Attention deficit-hyperactivity disorder; GAD, General anxiety disorder; SAD, Social anxiety disorder; PD, Panic disorder *When available; **Intranasal esketamine has been accepted by the FDA for therapy-resistant depression (Continued overleaf).

DRUG	DRUG CLASS	OFFICIAL INDICATION	PSYCHIATRIC DISORDER	RECOMMENDATION IN PSYCHIATRY*
Propranolol	β-blockers	High blood pressure, angina pectoris, atrial fibrillation, migraine, essential tremor	Anxiety disorders, PTSD prevention	Not recommended in GAD, SAD, or PD[62] Can be discussed in prevention of post-traumatic symptoms[68]
Rifampicin	Antibiotics	Infections	Depression	
S-adenosyl-L methionine	Substrate in different metabolic reactions	None	Depression	
Statins	Hypolipidemic drugs	Hypercholesterolemia, hypertriglyceridemia	Schizophrenia	
Tamoxifen	Chemotherapy	Breast cancer	Acute mania	As third-line treatment in acute mania[45]
T3	Thyroid hormone	Hypothyroidism	Unipolar and bipolar depression	As second-line adjunctive medication in treatment resistant depression[58] As third-line adjunctive treatment in bipolar depression[45]

Table I (Continued). Non-psychotropic drugs and their non-psychiatric and psychiatric uses. 5-HTP, L5-hydroxytryptophane; NAC, N-acethyl cysteine; NSAID, Nonsteroidal anti-inflammatory drug; ADHD, Attention deficit-hyperactivity disorder; GAD, General anxiety disorder; SAD, Social anxiety disorder; PD, Panic disorder *When available; **Intranasal esketamine has been accepted by the FDA for therapy-resistant depression.

efficacy or less tolerability, but can also highlight a lack of studies, in number and in quality. It is the case of gabapentin which is listed as first-line treatment in anxiety symptoms among bipolar patients, despite only level 3 evidence.[61] The β-blocker propranolol is not recommended in anxiety guidelines, because available data overall is against it for now.[62] Propranolol has been evaluated in many studies that do not reach expected quality level; there are few RCTs and most of them concern panic attacks and agoraphobia, for which a meta-analysis was not conclusive.[39]

Evidence-based medicine is intrinsically limited by availability of data. The example of lithium as a first choice in bipolar disorder is illustrative since this undisputed reference drug for bipolar disorder only has level 2 evidence in bipolar depression. Tamoxifen has level 2 evidence for treating acute mania, but with safety concerns and little clinical experience[63]; therefore, contrarily to lithium, it cannot be advised as first-line treatment. Concerning NSAIDs, a meta-analysis found positive results in depression, which would correspond at least to level 2 evidence; however, there are limitations due to the possibility of bias and to the heterogeneity of available studies. Moreover, the use of NSAIDs in psychiatry needs an extensive appreciation of safety concerns, notably about infectious risk.[64]

Guidelines are a good summary of what is rather well established at a given moment. But there are delays between the discovery of potential beneficial effects of a molecule in a neuropsychiatric disorder and their validation with the inclusion of the molecule in guidelines. Indeed, it takes time to finance and then perform quality studies, the results of which finally get included into guidelines. So-called preliminary data can sometimes remain a long time without confirmation, either positive or negative. So, with several non-PMs, such as bumetanide, minocycline, and rifampicin, as well as NSAIDs and SAMe, further trials are needed to establish their usefulness in psychiatric treatment.

These delays can be acceptable when other effective medications are available, but they can be distressing to patients and therapists for disorders with no known treatment.

Considering the case of AD, current guidelines recommend at least a try with cholinesterase inhibitors or NMDA antagonists, since there is no better alternative.[65] This encourages exploration of new drugs and it will be important to establish how much NSAIDs, rifampicin, or doxycycline really protect from AD or slow its evolution. The same is true for preventing the development of PTSD, with very few data available except rare but encouraging results for propranolol and hydrocortisone, which administered shortly after a trauma, favorably influence memory retrieval.[66,67] Propranolol, (but not hydrocortisone), has been listed in a guideline as an option to prevent the emergence of post-traumatic symptoms.[68]

While the primary focus of our review is on the potential role of several non-PMs on the evolution of psychiatric disorders, there are two other issues pertaining to the relevance of medical treatments to psychiatry, first, the improvement of psychiatric symptoms by treating non-psychiatric diseases, and, second, the prevention of neuropsychiatric syndromes by treating or preventing non-psychiatric diseases. Unfortunately, there are very few studies aimed at these clinically relevant questions.

As for the first issue, many physical diseases or disorders such as auto-immune diseases (lupus erythematosus, autoimmune encephalitis, etc), endocrine diseases, Parkinson disease and other neurological diseases, intoxications, metabolic diseases, infections, fever, dehydration, and many other situations induce psychiatric symptoms. Depending on their severity, these situations could be treated without PMs, ie, by improving the physical condition. Trials comparing psychiatric outcomes in non-PM groups with non-PM plus PM groups are lacking.

As to the second issue, which is relevant to psychiatric epidemiology, the question raised is whether treatment or prevention of given non-psychiatric diseases might delay or suppress the occurrence of neuropsychiatric syndromes: how do early interventions delay or prevent the physical disease and how could this prevent psychiatric complications? Examples are that the early detection of hypertension may reduce dementia prevalence.[69-71] Cardiovascular prevention based on known risk factors has potential beneficial effects on the incidence of psychiatric disorders. An epidemiological study did show a reduction of psychiatric hospitalization among patients receiving statins, L-type calcium channel antagonists, or biguanides.[56] But a causal link cannot be asserted. Were the findings a direct or indirect effect of the non-PMs on the psychiatric disorders? Do these non-PMs have clear psychotropic properties? And if so, what are these properties? Psychiatric patients often receive less care than they should; so, by receiving cardiovascular treatments, were these patients more exposed to also receiving treatment for psychiatric symptoms? There are also questions about the association between cardiovascular and psychiatric disorders and about how treating one may affect the other. Diabetes mellitus is highly associated with depression.[72] If untreated, it leads to cardiovascular complications, themselves associated with mood disorders or dementia. Obesity, the major risk factor for cardiovascular disorders, and a source of stigmatization among young people, shows a reciprocal link with depression.[73,74] Vaccination is among the best illustrations of how psychiatric symptoms can be prevented by internal medicine interventions. Vaccines protect against many infections that affect brain functions: tick-borne diseases, viral encephalitis, etc. In some cases, the relation between psychiatric disorders and nonpsychiatric diseases is reciprocal. For example, treatment of tobacco addiction decreases the prevalence of COPD, and a reduced prevalence of this severe physical disease lessens its psychiatric complications, notably depression.

We reviewed several non-PMs that already have or that could have a role in the practice of psychiatry. There is sufficient evidence for some non-PMs to be recommended in psychiatric guidelines, indicating that the pharmacological treatment of psychiatric disorders does not only rely on PMs. However, the lack of high-quality data remains the main issue for most of the indications of non-PMs in neuropsychiatric disorders. ■

Disclosure/Acknowledgments: The authors have no conflicts of interest.

References

1. Berk M, Dean O, Drexhage H, et al. Aspirin: a review of its neurobiological properties and therapeutic potential for mental illness. *BMC Med.* 2013;11-74.
2. Mendlewicz J, Kriwin P, Oswald P, Souery D, Alboni S, Brunello N. Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: a pilot open-label study. *Int Clin Psychopharmacol.* 2006;21(4),227231.
3. Savitz J, Preskorn S, Teague TK, Drevets D, Yates W, Drevets W. Minocycline and aspirin in the treatment of bipolar depression: a protocol for a proof-of-concept, randomised, double-blind, placebo-controlled, 2x2 clinical trial. *BMJ Open.* 2012;2(1):e000643. doi:10.1136/bmjopen-2011-000643.
4. Rosenblat JD, Kakar R, Berk M, et al. Anti-inflammatory agents in the treatment of bipolar depression: a systematic review and meta-analysis. *Bipolar Disord.* 2016;18(2):89-101.
5. Köhler O, Benros ME, Nordentoft M, et al. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry.* 2014;71(12):1381–1391.
6. Husain MI, Strawbridge R, Stokes PR, Young AH. Anti-inflammatory treatments for mood disorders: Systematic review and meta-analysis. *J Psychopharmacol.* 2017;31(9),11371148.
7. Laan W, Grobbee DE, Selten JP, Heijnen CJ, Kahn RS, Burger H. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry.* 2010;71(5),520527.
8. Deardorff WJ, Grossberg GT. Targeting neuroinflammation in Alzheimer's disease: evidence for NSAIDs and novel therapeutics. *Exp Rev Neurother.* 2017;17(1),1732.
9. Nevado-Holgado AJ, Lovestone S. Determining the molecular pathways underlying the protective effect of non-steroidal anti-inflammatory drugs for Alzheimer's disease: A bioinformatics approach. *Comput Struct Biotechnol J.* 2017;15:1-7.
10. Lemonnier E, Villeneuve N, Sonie S, et al. Effects of bumetanide on neurobehavioral function in children and adolescents with autism spectrum disorders. *Transl Psychiatry.* 2017;7(3):e1056. Published 2017 Mar 14. doi:10.1038/tp.2017.10.
11. Lemonnier E, Lazartigues A, Ben-Ari Y. Treating schizophrenia with the diuretic bumetanide: a case report. *Clin Neuropharmacol.* 2016;39(2):115-117.
12. Rahmanzadeh R, Shahbazi A, Ardakani MK, Mehrabi S, Rahmanzade R, Joghateaei MT. Lack of the effect of bumetanide, a selective NKCC1 inhibitor, in patients with schizophrenia: a double-blind randomized trial. *Psychiatry Clin Neurosci.* 2017;71(1):72-73.
13. Lowry JA, Brown JT. Significance of the imidazoline receptors in toxicology. *Clin Toxicol (Phila).* 2014 Jun;52(5):454-69.
14. Attention deficit hyperactivity disorder : diagnosis and management. Available at : https://www.nice.org.uk/guidance/ng87/chapter/Recommendations#medication NICE guidelines. Accessed April 18, 2019.
15. Naguy A. Clonidine use in psychiatry: panacea or panache. *Pharmacology.* 2016;98(1-2):87-92.
16. Fiore MC, Jaén CR, Baker TB, et al. Treating tobacco use and dependence: 2008 update. *Clinical Practice Guideline.* Rockville, MD: US Department of Health and Human Services, Public Health Service; 2008.
17. Kung S, Espinel Z, Lapid MI. Treatment of nightmares with prazosin: a systematic review. *Mayo Clin Proc.* 2012;87(9):890-900.
18. Berlin RK, Butler PM, Perloff MD. Gabapentin therapy in psychiatric disorders: a systematic review. *Prim Care Companion CNS Disord.* 2015;17(5):10.4088/PCC.15r01821. doi:10.4088/PCC.15r01821.
19. Culpepper L, Wingertzahn MA. Over-the-counter agents for the treatment of occasional disturbed sleep or transient insomnia: a systematic review of efficacy and safety. *Prim Care Companion CNS Disord.* 2015;17(6):10.4088/PCC.15r01798. Published 2015 Dec 31. doi:10.4088/PCC.15r01798.
20. Guaiana G, Barbui C, Cipriani A. Hydroxyzine for generalised anxiety disorder. *Cochrane Database Syst Rev.* 2010;(12):CD006815. PMID: 21154375.
21. Iadarola ND, Niciu MJ, Richards EM et al. Ketamine and other N-methyl-D-aspartate receptor antoagnonists in the treatment of depression: a perspective review. *Ther Adv Chronic Dis.* 2015;6(3):97-114.
22. FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632761.htm Food and Drug Administration. Accessed April 8, 2019.
23. Kishi T, Matsunaga S, Oya K, Nomura I, Ikuta T, Iwata N. Memantine for Alzheimer's disease: an updated systematic review and meta-analysis. *J Alzheimers Dis.* 2017;60(2):401-425.
24. Garido-Mesa N, Zarzuelo A, Galvez J. Minocycline: far beyond an antibiotic. *Br J Pharmacol.* 2013;169(2):337-352.
25. Rosenblat JD, McIntyre RS. Efficacy and tolerability of minocycline for depression: a systematic review and meta-analysis of clinical trials. *J Affect Disord.* 2018; 227:219-225.
26. Savitz JB, Teague TK, Misaki M, et al. Treatment of bipolar depression with minocycline and/or aspirin: an adaptive, 2×2 double-blind, randomized, placebo-controlled, phase IIA clinical trial. *Transl Psychiatry.* 2018;8(1):27. doi:10.1038/s41398-017-0073-7.
27. Murrough JW, Huryk KM, Mao X, et al. A pilot study of minocycline for the treatment of bipolar depression: effects on cortical glutathione and oxidative stress in vivo. *J Affect Disord.* 2018;1;230:56-64.
28. Deaking B, Suckling J, Barnes TRE, et al. The benefit of minocycline on negative symptoms of schizophrenia in patients with recent-onset psychosis (BeneMin): a randomized, double-blind, placebo-controlled trial. *Lancet Psychiatry.* 2018;5(11):885-894.
29. Levkovitz Y, Mendlovich S, Riwkes S, et al. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. *J Clin Psychiatry.* 2010;71(2):138-148.
30. Xiang YQ, Zheng W, Wang SB, et al. Adjunctive minocycline for schizophrenia: a meta-analysis of randomized controlled trials. *Eur Neuropsychopharmacol.* 2017;27(1):8-18.
31. Umeda T, Ono K, Sakai A, et al. Rifampicin is a candidate preventive medicine against amyloid-beta and tau oligomers. *Brain.* 2016;139:1568-1586.
32. Yulug B, Hanoglu L, Ozansov M, et al. Therapeutic role of rifampicin in Alzheimer's disease. *Psychiatry Clin Neurosci.* 2018;72(3):152-159.
33. Loeb MB, Molloy DW, Smieja M, et al. A randomized, controlled trial of doxycycline and rifampin for patients with Alzheimer's disease. *J Am Geriatr Soc.* 2004;52:381-387.
34. Iizuka T, Morimoto K, Sasaki Y et al. Preventive effect of rifampicin on Alzheimer disease needs at least 450 mg daily for 1 year: an FDG-PET follow-up study. *Dement Geriatr Cogn Dis Extra.* 2017;7:201-214.
35. Molloy DW, Standish TI, Zhou Q, Guyatt G, DARAD Study group. A multicenter, blinded, randomized, factorial controlled trial of doxycycline and rifampin for treatment of Alzheimer's disease: The DARAD trial. *Int J Geriatr Psychiatry.* 2013;28: 463–470.
36. Lizuka T, Morimoto K, Sasaki Y et al. Preventive effect of rifampicin on Alzheimer disease needs at least 450 mg daily for 1 year: an FDG –PET follow-up study. *Dement Geriatr Cogn Dis Extra.* 2017;7(2):204-214.
37. Peterson TC, Brown IR. Cysteamine in combination with N-acetylcysteine prevents acetaminophen-induced hepatotoxicity. *Can J Physiol Pharmacol.* 1992;70(1):20-8.
38. Minarini A, Ferrari S, Galleti M, et al. N-acetylcysteine in the treatment of psychiatric disorders: current status and future prospects. *Expert*

Opin Drug Metab Toxicol. 2017;13(3):279-292.
39. Deepmala, Slattery J, Kumar N et al. Clinical trials of N-acetylcysteine in psychiatry and neurology: a systematic review. *Neurosci Biobehav Rev.* 2015;55:294-321.
40. Zhen W, Zhang QE, Cai DB, et al. N-acetylcysteine for major mental disorders: a systematic review and meta-analysis of randomized controlled trials. *Acta Psychiatr Scand.* 2018,137(5):391-400.
41. Sharma A, Gerbarg P, Bottiglieri T, et al. S-Adenosylmethionine (SAMe) for neuropsychiatric disorders: a clinician-oriented review of research. *J Clin Psychiatry.* 2017;78(6):e656-e667.
42. Shaw K, Turner J, Del Mar C. Tryptophan and 5-hydroxytryptophan for depression. *Cochrane Database Syst Rev.* 2002;(1):CD003198.
43. Hori H, Kunugi H. Dopamine agonist-responsive depression. *Psychogeriatrics*. 2016;13(3):89-95.
44. Corrigan MH, Denahan AQ, Wright CE, Ragual RJ, Evans DL. Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. *Depress Anxiety.* 2000;11(2):58-65.
45. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN. Canadian Network for mood and anxiety treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord.* 2018;20(2):97-170.
46. Shingu K, Kawai I, Yamada K. Thee cases of unipolar delusional depression responsive to L-dopa. *Folia Psychiatr Neurol Jpn.* 1979;33(4):511-515.
47. Koella WP. CNS-related (side-)effects of beta blockers with special reference to mechanisms of action. *Eur J Clin Pharmacol.* 1985;28(Suppl):55-63.
48. Cruickshank JM: The clinical importance of cardioselectivity and lipophilicity in beta blockers. *Am Heart J.* 1980;100:160-178.
49. Ravaris CL, Friedman MJ, Hauri PJ, McHugo GJ. A controlled study of alprazolam and propranolol in panic-disordered and agoraphobic outpatients. *J Clin Psychopharmacol.*1991;11(6):344-350.
50. Steenen SA, van Wijk AJ, van der Heijden GJ, van Westrhenen R, de Lange G, de Jongh A. Propranolol for the treatment of anxiety disorders: systematic review and meta-analysis. *J Psychopharmacol.* 2016;30(2):128-139.
51. Lonergan MH, Olivera-Figueroa LA, Pitman RK, Brunet A. Propranolol's effects on the consolidation and reconsolidation of long-term emotional memory in healthy participants: a meta-analysis. *J Psychiatry Neurosci.* 2013;33(4):222-231.
52. Burbiel JC. Primary prevention of posttraumatic stress disorder: drugs and implications. *Mil Med Res.* 2015;2:24. doi:10.1186/s40779-015-0053-2.
53. Brunet A, Orr SP, Tremblay H, Robertson K, Nader K, Pitman RK. Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driver traumatic imagery in post-traumatic stress disorder. *J Psychiatr Res.* 2008;42(6):503-506.
54. Brunet A, Saumer D, Lia A, Streiner Dl, Tremblay J, Pitman RK. Reduction of PTSD symptoms with pre-reactivation propranolol therapy : a randomized controlled trial. *Am J Psychiatry.* 2018:175(5) :427-433.
55. Shen H, Li R, Yan R, et al. Adjunctive therapy with statins in schizophrenia patients : a meta-analysis and implications. *Psychiatry Res.* 2018;262:84-93.
56. Hayes JF, lundi A, Wicks S, et al. Association of hydroxylmethyl glutaryl coenzymes A reductase inhibitors, L-type calcium channel antagonists, and biguanides with rates of psychiatric hospitalization and self-harm in individuals with serious mental illness. *JAMA Psychiatry.* 2019;76(4):382-390.
57. El-Hage W, Leman S, Camus V, Belzung C. Mechanisms of antidepressant resistance. *Front Pharmacol.* 2013;4:146.
58. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. *Pharmacological Treatments. Can J Psychiatry.* 2016;61(9):540-560.
59. Touma KTB, Zoucha AM, Scarff JR. Liothyronine for depression: a review and guidance for safety monitoring. *Innov Clin Neurosci.* 2017;14(3-4):24-29.
60. Parmentier T, Sienaert P. The use of triiodothyronine (T3) in the treatment of bipolar depression: A review of the literature. *J Affect Disord.* 2018;229:410-414.
61. Schaffer A, McIntosh D, Goldstein BI, et al. The canadian network for mood and anxiety reatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid anxiety disorders. *Ann Clin Psychiatry.* 2012;24(1):6-22.
62. Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry.* 2014;14(Suppl 1):S1.
63. Yildiz A, Nikodem M, Vieta E, Correll CU, Baldessarini RJ. A network meta- analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania. *Psychol Med.* 2015;45:299-317.
64. Anti-inflammatoires non stéroïdiens (AINS) et complications infectieuses graves – Point d'information. Available at: https://ansm.*sante*.fr/S-informer/Actualite/Anti-inflammatoires-non-steroidiens-AINS-et-complications-infectieuses-graves-Point-d-Information ANSM. Accessed April 18, 2019.
65. Massoud F, Gauthier S. Update on the pharmacological treatment of Alzheimer's disease. *Curr Neuropharmacol.* 2010; 8(1):69-80.
66. Qi W, Gevonden M, Shaly A. Preventionof post-traumatic stress disorder after trauma : current evidence and future directions. *Curr Psychiatry Rep.* 2016; 18-20.
67. Sijbrandij M, Kleiboer A, Bisson JI, Barbui C, Cuijpers P. Pharmacological prevention of post-traumatic stress disorder and acute stress disorder: a systematic review and meta-analysis. *Lancet Psychiatry.* 2015;2(5):413-421.
68. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol.* 2014;28(5) :403-349.
69. De la Torre JC. Cerebral perfusion enhancing interventions: a new strategy for the prevention of Alzheimer Dementia. *Brain Pathol.* 2016;26(5):618-631.
70. De la Torre JC. Carotid artery ultrasound and echocardiography testing to lower the prevalence of Alzheimer's disease. *J Stroke Cerebreovasc Dis.* 2009;18(4):319-28.
71. Coca A, Monteagudo E, Coménech M, Camafort M, Sierra C. Can the treatment of hypertension in the middle-aged prevent dementia in the elderly? *High Blood Press Cardiovasc Prev.* 2016;23(2):97-104.
72. Elamoshy R, Bird Y, Thorpe L, Moraros J. Risk of depression and suicidality among diabetic patients: a systematic review and meta-analysis. *J Clin Med.* 2018;7(11):445. doi:10.3390/jcm7110445.
73. Harriger JA, Thompson JK. Psychological consequences of obesity: weigh bias and body image in overweight and obese youth. *Int Rev Psychiatry.* 2012;24(3):247-253.
74. Rajan TM, Menon V. Psychiatric disorders and obesity: a review of association studies. *J Postgrad Med.* 2017;63(3):182-190.