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- **Proper Use of Common Psychiatric Drugs in Nonpsychiatric Practice**
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Professor Daiga Helmeste*
- **Continuous Dopaminergic Stimulation and Parkinson's Disease Treatment**
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After treatment

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Response: the tumor in total regression upon one month treatment



Before treatment



After treatment

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Editorial

In this issue, we present some excellent articles in Psychiatry and Neurology. Traditionally, functional psychiatric illness is distinguished from neurological conditions in that in the former, gross structural lesions are not detectable in the brain.

However, with the refinement of investigational tools, we now have increasing knowledge regarding anatomical and pathophysiological changes in conditions such as mood disorders and schizophrenia. For example, in major depressive disorder, there is loss of neurons in the hippocampus, reduction in volume of the amygdala, and reduction in gray matter volume in the prefrontal cortex. On the other hand, in conditions traditionally regarded as neurological in nature, such as Parkinson's disease, the importance of psychiatric disability is increasingly being recognized. Recent studies have revealed the close relationship of the two specialties dealing with disorders of the brain. We expect the division between Psychiatry and Neurology to be blurred further as we better understand the working of this important human organ. More collaboration between both specialties is expected to yield fruitful results in future research.



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Dr Lee Wing King (李永堅醫生)

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Proper Use of Common Psychiatric Drugs in Nonpsychiatric Practice



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Key words:

Psychiatric drugs (精神科藥物), nonpsychiatric settings (非精神科環境), antidepressants (抗抑鬱藥), benzodiazepines (苯二氮卓類藥物)

Introduction

Anxiety and depression are commonly seen, especially in family medicine, cardiology, gastroenterology, oncology, rheumatology and geriatric settings. For example, many chest discomforts are related to anxiety, while gastrointestinal complaints often have an emotional component. Psychosomatic disorders are common. Pains and aches generally improve with antidepressants and anti-anxiety drugs, no matter what the original causes are. The emotional problems of many of these patients can be effectively managed in nonpsychiatric settings with some knowledge and training in the proper use of psychiatric drugs.

Benzodiazepines

Many physicians tend to prescribe benzodiazepines when they perceive slight anxiety or unhappiness in patients. Benzodiazepines commonly prescribed in nonpsychiatric settings include the now obsolete ones with long half-life and high potential for dependence, such as diazepam (Valium), chlordiazepoxide (Librium), triazolam (Halcion), flurazepam (Dalmane) and flunitrazepam (Rohypnol). In recent years, shorter-acting preparations such as alprazolam (Xanax), bromazepam (Lexotan), clonazepam (Klonopin, Rivotril), lorazepam (Ativan), midazolam (Dormicum) and nitrazepam (Mogadon) have generally replaced the old ones. Many of these benzodiazepines with shorter half-life are also commonly used by physicians as hypnotics or night sedation. The newer atypical benzodiazepines with much less potential for dependence and very short half-life, such as zolpidem (Stilnox, Ambien) and zopiclone (Imovane), are now popular hypnotics.

Antidepressants

Antidepressants are also commonly prescribed in nonpsychiatric settings. First-generation tricyclic antidepressants (TCAs) such as amitriptyline (Elavil), imipramine (Tofranil), clomipramine (Anafranil), doxepin (Sinequan), nortriptyline (Aventyl) and desipramine (Norpramin) and the monoamine oxidase inhibitors (MAOIs) such as phenelzine (Nardil) have been replaced by second-generation antidepressants with much fewer side effects in most nonpsychiatric settings. These second-generation antidepressants include the specific serotonin uptake (5HT) inhibitors (SSRIs) such as fluoxetine (Prozac), paroxetine (Seroxat),¹ sertraline (Zoloft), citalopram (Cipram) and escitalopram (Lexapro),² and the serotonin-norepinephrine (5HT, NE) reuptake inhibitors (SNRIs) such as venlafaxine (Effexor), duloxetine (Cymbalta),³ and desvenlafaxine (Pristiq), which is a metabolite of the parent venlafaxine.

Other Psychiatric Drugs

Antipsychotic drugs include the now obsolete neuroleptics (dopamine [DA] antagonists) such as chlorpromazine (Largatil), haloperidol (Haldol), thioridazine (Melleril), trifluoperazine (Stelazine) and thiothixene (Navane). These drugs with troublesome side effects should no longer be prescribed in nonpsychiatric settings, but patients from third-world countries and government clinics might still be given these drugs. New atypical antipsychotics containing 5HT action in addition to their DA antagonist property are much better replacements. Examples include risperidone (Risperdal), quetiapine (Seroquel), olanzapine (Zyprexa), ziprasidone (Geodon, Zeldox), sertindole (Serdolect) and the partial DA agonist aripiprazole (Abilify).⁴ In addition to schizophrenia,

patients suffering from bipolar disorders may be prescribed these atypical antipsychotics by their psychiatrists, but weight gain or metabolic syndrome are problematic side effects that need attention.

Flupentixol/melitracen (Deanxit) is an antipsychotic/TCA combination for anxiety and depression and is quite popular in nonpsychiatric settings. Antipsychotic augmentation is often useful for patients not responding to antidepressant treatment, and the efficacy of flupentixol/melitracen seen by many patients and physicians in nonpsychiatric settings may be related to the “built-in” augmentation function through the combined antipsychotic antidepressant mechanism.

Lithium is frequently encountered by physicians in nonpsychiatric settings. Use of lithium requires some training and periodic monitoring of blood level.⁵ It is not a dangerous drug as many physicians were led to believe.

Drugs for dementia are also frequently encountered. These include the first-generation acetylcholine esterase inhibitors such as donepezil (Aricept) and rivastigmine (Exelon) with side effects due to the resulting acetylcholine accumulation, and the new N-methyl-D-aspartate (NMDA) glutamate modulator memantine (Ebixa) with much fewer side effects.

Common Misconceptions and Mistakes in Using Psychiatric Drugs in Nonpsychiatric Settings

Modern psychiatric drugs are generally safe when used properly. The chronic and often fluctuating nature of many emotional problems is the basis for some poor habits seen in nonpsychiatric settings. Impatience on the part of patients or physicians may lead to premature drug switching without first optimizing dosages. As response takes time, physicians need to ensure compliance and be patient, rather than switch drugs prematurely on patients' requests.

Unhappiness is Different From Pharmacologically Treatable Depression and Anxiety

Antidepressants and anti-anxiety drugs should be used with a clear goal and plan. They should be prescribed in full dosages and for a long enough duration. Several days' treatment with a few tablets of antidepressants or anti-anxiety drugs may remove some anxiety, but will not remove true depression or create happiness. Prescriptions should be given with a clear endpoint in mind.

Do not Prescribe Anti-depressants in Small Doses

Many untrained physicians prescribe antidepressants in very small doses and have the illusion that even small doses are effective in relieving depression. They are not. If a patient responded to a very small dose of antidepressant, chances were that he or she did not require the drug in the first place. Thus, when using antidepressants, use the full dose and treat for adequate duration. Most modern SSRIs and SNRIs can be escalated to full dosage in a few days.

Personality or Mind Changing Properties of Psychiatric Drugs

Some antidrug activists or overworried family members claim that psychiatric drugs may create an artificial personality, artificial “unhappiness”, or cause a person to lose his true mind. They do not. When used properly, not only do they not change the patient as a person, but they bring back one's premorbid self and rectify the pathological thought processes.

Treatment Duration

Treatment durations for antidepressants and benzodiazepines are quite different. Antidepressants should be prescribed in full dose and be maintained for a long enough duration, generally 1 year for a first depression episode and lifelong when it is proven to be of a recurrent and severe nature. Anti-anxiety drugs such as benzodiazepines should only be used for a defined short period of time, generally not exceeding 1–2 weeks and never over several months. They should be used in minimum doses. Benzodiazepine type anti-anxiety drugs should be replaced by

antidepressants of the SSRI type after the initial 1–2 weeks of treatment. Physicians should avoid prescribing benzodiazepines in bottles containing weeks or months of supplies.

Do Different Antidepressants Differ in Efficacy?

Naturally physicians in nonpsychiatric settings would prefer to keep only a small number of psychiatric drugs in their clinics. Despite vigorous promotional efforts from drug companies boasting superior efficacy, reduced side effects or improved formulations of their products, the efficacy of most second-generation antidepressants does not differ in a major way except that a number of recent reviews showed escitalopram (Lexapro) to be superior to others when all SSRIs and SNRIs were compared.^{6–10} However, antidepressants differ much in terms of side effects and cytochrome P450 (CYP) enzyme inhibition potential,^{11,12} which should guide treatment choice. In nonpsychiatric settings, it is better for physicians to become familiarized with a small number of psychiatric drugs rather than switching the patient quickly between different SSRIs or SNRIs with the unrealistic hope that a drug with superior efficacy will be eventually found. Despite much expectation, personalized medicine is still only a dream as far as antidepressants are concerned.¹²

The patient should be referred to a psychiatrist after unsuccessful attempts of using two different antidepressants. Research indicates that after two trials of two different antidepressants, the chance of success with a third one is not great. It is also important to consider early referral when in doubt. Early optimal treatment translates into early recovery, which is important for both patients and their families.

One of the commonest misunderstandings about antidepressant choices concerns separation of reuptake inhibitors into so-called dual- and single-action antidepressants. Marketing efforts often advertise dual reuptake (serotonin and norepinephrine) inhibitors as more effective than single reuptake inhibitors. However, evidence has failed to support this as stated above. The forgotten pharmacological fact is that the old TCAs consisted of both dual reuptake

Table 1. Summary

Training:	
a.	Take short courses on the use of psychiatric drugs (many available through HKMA and various academic and professional societies) and attend refresher courses for updates periodically. Interactive CME courses have been shown more effective than didactic lectures or prints.
b.	Use and gain experience in only a small number of drugs. Go beyond the drug names and know them very well (their pharmacology including side effects and adverse effects, FDA warnings). In nonpsychiatric settings, avoid substituting branded products with generics to remove uncertainties in quality control, bioavailability and psychological effect in case patient's clinical condition changed.
For antidepressant drugs:	
a.	To begin, use those with the least potential for CYP enzyme inhibition and therefore least potential for drug-drug interactions (eg, citalopram, escitalopram, sertraline, venlafaxine, duloxetine).
b.	Use those with simple dosage schedules (eg, 10 mg, 20 mg, 60 mg daily in one single dose) and least side effects to encourage compliance (eg, citalopram, escitalopram, sertraline, duloxetine).
c.	Escalate dosage to full recommended dose in a few days and maintain for at least 4–6 weeks, and wait for response. Warn patient in advance about possible side effects (eg, sedating side effects of mirtazapine) to encourage compliance.
c.	If no response after two different antidepressant trials, do not rotate to a third one. Refer for psychiatric consultation early to avoid delay in treatment.
For benzodiazepines:	
a.	Use the smallest possible dose. Do not be afraid to use only half or a quarter of a company-recommended dose or tablet. Encourage the patient to accept less than optimal sedation to avoid dependence, which can occur quickly (eg, after 1 week).
b.	Use benzodiazepines for a limited duration (eg, 2 weeks and no longer than 1 month; begin to tail dose after obtaining initial benefit) and prepare the patient for this action.
c.	Do not use benzodiazepines for chronic anxiety. Replace benzodiazepines with SSRI antidepressants if anxiety is seen as chronic.
d.	For elderly patients, caution should be given on possible falls, confusion, and memory loss or other cognitive impairment.
e.	Avoid using long-acting benzodiazepines as much as possible.
f.	Do not use benzodiazepines to treat unhappiness or depression. None of them are effective.

inhibitors (such as amitriptyline and imipramine) and single reuptake inhibitors (such as desipramine and nortriptyline). TCAs have been in the market for a long time, and it is common knowledge that they do not differ from each other in terms of efficacy. Commercial marketing efforts simply ignored this fact and encouraged uninformed physicians to believe that inhibiting more different types of neurotransmitters is better. The failure of triple reuptake inhibitors (5HT, NE and DA) developed as more efficacious antidepressants further showed that more is not necessarily better.

After patent expiration, it is a common practice for the industry to repackage the compound in different formats such as extended release or different dosages, or to rename a metabolite of the parent drug and market it as possessing fewer side effects or less CYP enzyme inhibition property. Again, one

should remember that different formats of the same drug do not translate into different efficacy.

Precautions

In general, new-generation antidepressants are quite safe. Compared with the old TCAs, their margin of safety is much larger. In overdose situations where TCAs could be fatal, the new SSRIs carry a much lower risk of fatality.

Risks with benzodiazepines include dependence, falls and cognitive impairment in the elderly when used chronically. Textbooks caution about using benzodiazepines and regard them as dangerous drugs. In reality, the very small doses used by many physicians for night time sedation and anxiety in younger patients generally do not carry serious risks for cognitive impairment.

Symptomatic vs Core Pathology

The major problem with benzodiazepines is that while they offer fast symptomatic relief and mask emotional disturbances, they do not address the core pathology of emotional disorders. Antidepressants, by contrast, appear to reverse depression and anxiety. An analogy is the use of antipyretics in fever caused by a bacterial infection. While antipyretics give quick symptomatic relief, antibacterial drugs should in fact be used and not antipyretics alone.

Drug-drug Interactions

An important precaution in the use of antidepressants is the potential for drug-drug interactions, especially in the elderly where polypharmacy is frequently the norm. Some antidepressants are potent CYP enzyme inhibitors, notably 3A4, CYP 2D6, 2C9 and 2C19. For SSRIs, there are potential risks for drug-drug interactions with erythromycin, ketoconazole, tamoxifen and antiarrhythmics (through 3A4); miconazole and S-warfarin (through 2C9); propranolol, diazepam, clomipramine (through 2C19); antiarrhythmics, beta-blockers, haloperidol and neuroleptics (through 2D6). Additionally, in cultures where herbal medications or alcohol consumption are common, appropriate warnings about drug-drug interactions are needed.

Adverse Effects

There are few serious adverse effects with new antidepressants and benzodiazepines. Agitation with SSRIs in the initial stage is generally dose-related and also related to anxiety towards Western drugs among Chinese patients. With advance warning and a smaller starting dose in drug-anxious patients, drug-related agitation is manageable. Serious agitation plus restlessness, sweating, abnormal eye rolling, fever and general weakness should alert one to the possibility of serotonin syndrome, which is rarely encountered in nonpsychiatric settings but should be an important caution item for physicians using these drugs. Otherwise, gastrointestinal and sleep disturbances are easily manageable side effects. Increase in suicidal ideation is a warning in the use of antidepressants in younger patients. Physicians using antidepressants

in younger patients should keep this in mind.

Generic Substitution or Drug Switching

In nonpsychiatric settings, when the patient has become stable, it is advisable not to substitute a branded psychiatric drug with a generic one simply because of costs. Some generic drugs exhibit dubious or inconsistent bioavailability, and their quality is an important uncertainty to be excluded in the management of a chronic illness. Drug substitution introduces a difficult and important factor when the mental status profile of the patient begins to change after switching. Emotional disorders are generally chronic in nature and are also subject to the influence of a variety of life events and stress. It may be difficult to assess the fluctuation in symptoms and to know if the change in mental status is related to the quality of the substitution.

Conclusion

New antidepressants such as SSRIs and SNRIs are useful and safe in nonpsychiatric settings. Problems of emotion, such as depression and anxiety, accompany many medical disorders. Many emotional disorders also manifest themselves as physical disorders. Accepting that many patients do not wish to be referred to psychiatrists, the use of psychiatric drugs in nonpsychiatric settings should be encouraged, and their proper use should be promoted through education.

Proper use of psychiatric drugs in nonpsychiatric settings not only reduces the burden on the resource-strained psychiatric facilities, but also facilitates early treatment of emotional disorders and early intervention for medical complaints of psychological origin. Educational efforts should be aimed at the dissipation of misconceptions about psychiatric drugs, separation of drug-treatable and

drug-nontreatable emotional disorders, and caution about side effects and serious adverse effects.

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Continuous Dopaminergic Stimulation and Parkinson's Disease Treatment



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Key words:

Parkinson's disease (帕金森症),
dopamine (多巴胺)

Introduction

Since its first introduction in late 1960s, levodopa has been the time-tested medication for symptomatic treatment of Parkinson's disease (PD), and is highly effective in the treatment of motor symptoms. However, long-term levodopa therapy will inevitably lead to motor fluctuations and dyskinesias. Typically, these occur after 4 to 6 years of therapy, and affect approximately half of all patients.¹ Thereafter, the incidence increases by 10% per year as the disease progresses. Dopamine neurons fire continuously, and there is continuous activation of dopamine receptors in healthy brains. In the dopamine-depleted state, levodopa

or other short-acting dopaminergic drugs induce molecular changes and alter neuronal firing patterns in basal ganglia neurons, leading to motor complications. The concept of continuous dopaminergic stimulation proposes that continuous delivery of a dopaminergic drug will prevent pulsatile stimulation and avoid motor complications.²

Pathophysiology

Approximately 80% of the striatal nerve terminal and up to 60% of dopaminergic neurons in the substantia nigra must be lost before clinical symptoms of parkinsonism become apparent.³ This is due to

the compensatory mechanisms, which include an increase in dopaminergic activity in the substantia nigra, down-regulation of dopamine transporters, and upregulation of postsynaptic dopamine receptors in the striatum.⁴ Under normal physiological conditions, dopamine neurons have relatively constant rates of tonic activity. There is increased firing with rewards or an unexpected stimulus. Reuptake into presynaptic terminals ensures that extracellular concentrations of dopamine remain constant. Advancing disease results in fewer remaining striatal dopamine terminals and, consequently, decreased capacity to buffer fluctuations in dopamine levels. Thus, disease severity contributes to pulsatile stimulation of dopamine receptors in downstream neurons and consequent alterations in neuronal firing patterns that are thought to underlie the development of motor complications.

In addition to an increased sensitivity to fluctuating dopamine levels because of loss of nigral neurons, exposure to variable levels of a dopaminergic agent also contributes to fluctuations. In the early stages of oral levodopa treatment, patients with PD experience extensive benefit from the drug. However, with chronic treatment, the duration of benefit after each dose becomes progressively shorter. Patients begin to experience fluctuations in motor response, alternating between on response with a good anti-parkinson effect and off response when levodopa does not adequately control motor symptoms. Fluctuations may also occur in nonmotor symptoms such as psychological, autonomic and sensory symptoms. This occurs because the degenerating dopaminergic terminals are no longer able to adequately buffer the exogenous levodopa. Whilst degeneration continues, synaptic dopamine levels fluctuate with dosing of oral levodopa, leading to supraphysiological levels after dosing, followed by a dopamine-depleted state towards drug clearance.⁵ Dopamine receptors are thus stimulated in an abnormal intermittent fashion, inducing molecular changes within the striatum and other parts of the brain.

Pulsatile stimulation of striatal dopamine receptors can induce molecular and neurophysiological changes in striatal

neurons that are associated with dyskinesias. Studies in dopamine-denervated animals showed that dyskinesia induced by short-acting dopaminergic drugs is associated with altered expression of various genes or proteins, similar to those reported in postmortem brains of patients with PD. Neither the gene changes nor the dyskinesia associated with a short-acting dopaminergic drug are reported when the same drug is given by continuous infusion. The neurophysiological firing pattern of basal-ganglia neurons is also influenced by pulsatile dosing with a dopaminergic drug. Changes in the number and duration of pauses and bursts as well as firing frequency have been reported in both 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys and patients with PD. Furthermore, pulsatile administration of levodopa substantially changes external globus pallidus (GPe) to internal globus pallidus (GPi) firing-rate ratios, does not fully eliminate synchronous firing, and impairs mechanisms involved in long-term depression and striatal plasticity. How precisely these molecular and physiological changes lead to dyskinesia is not clearly understood.

“Continuous enteral infusion of a water-soluble form of levodopa reduced both off periods and dyskinesias”

Concept of Continuous Dopaminergic Stimulation

Given this evidence, continuous administration of levodopa may produce a constant supply of dopamine to the striatal dopaminergic receptors and mimic the

state seen during normal tonic firing of dopaminergic neurons. This would avoid the fluctuations in dopamine levels that normally accompany intermittent oral levodopa dosing, and thereby facilitate a more normal control of movement.⁶

Continuous dopaminergic stimulation can be achieved through continuous enteral infusion of a water-soluble form of levodopa. This technique reduced both off periods and dyskinesias in clinical studies.⁷ Other methods used for achieving continuous dopaminergic stimulation with variable success include sustained-release levodopa, increased frequency of dosing, long-acting dopamine agonists, and catechol-O-methyl transferase (COMT) inhibitors.

Advantages and Disadvantages of Continuous Enteral Infusion

The main advantage of continuous duodenal infusion is that it provides continuous delivery of levodopa, so that plasma concentrations of the drug can be kept nearly constant, thus reducing motor complications. Levodopa is an acidic drug and needs to be given with a large volume of fluid; thus, dermal administration is not practical.

The beneficial effects of continuous levodopa infusion on motor fluctuations and dyskinesias arise because it bypasses erratic gastric emptying in PD patients, which in turn increases the amount available in the nervous system. Titration of levodopa dosage is easy with this method. Another advantage is that other PD medications such as oral levodopa and dopamine agonists can be eliminated when this method is used.

Duodenal levodopa administration has several disadvantages. Firstly, a surgical procedure or percutaneous endoscopic gastrostomy is required for the placement of a small tube to the duodenum. Secondly, the accompanying pump may be cumbersome for some patients. Secondary effects may also occur, which include sporadic blockage of tubes, displacement of the inner tube, leakage at the tube connection, and local infections. Finally, high cost may be a limiting factor. One clinical study employed a stable suspension of levodopa and carbidopa (Duodopa™).⁸ All patients experienced a general improvement after the introduction

of continuous treatment. No severe complications were reported. A follow-up study showed a continued positive effect after 4–7 years of continuous duodenal infusion.⁹ Based on similar studies, some authors even propose continuous duodenal levodopa over apomorphine or subthalamic nucleus deep brain stimulation (STN-DBS). Unfortunately, this treatment modality is not yet available locally, but subcutaneous apomorphine, transdermal rotigotine and prolonged-release ropinirole are on the market.

Subcutaneous Apomorphine

Apomorphine, a nonergot derivative, is a potent, direct-acting dopamine receptor agonist. Apomorphine has a high affinity to D4 receptors, a lower affinity to D2, D3 and D5, and a lowest affinity to D1-like dopamine, serotonin and adrenoceptors. Subcutaneous apomorphine provides rapid, effective relief of off episodes associated with advanced PD.¹⁰ It is effective for rapid rescue from hypomobility, with a magnitude of motor improvement similar to that of levodopa. The effect begins within 20 minutes after dosing and lasts approximately 100 minutes. Therapeutic rescue doses are 2–6 mg, and patients typically require approximately three rescue doses per day.

A prospective study has confirmed marked dyskinesia reduction with continuous subcutaneous apomorphine therapy. This supports the concept that replacement of short-acting oral antiparkinsonian medications with continuous dopamine receptor stimulation may reverse, at least partially, the sensitization process believed to mediate the development of drug-induced dyskinesia in PD. However, apomorphine is associated with a clinically significant potential to cause nausea and orthostatic hypotension, as well as psychiatric complications.¹¹

Apomorphine warrants wider application in treating advanced PD, but its use is restricted by the high cost, the necessity of concomitant treatment for prevention of side effects, the subcutaneous administration, and the side effects.

Transdermal Rotigotine

Rotigotine is a lipid-soluble, nonergot, D3, D2, D1 dopamine receptor agonist that has demonstrated efficacy as an alternative therapeutic option in both early and advanced PD.¹² It is uniquely formulated as a transdermal patch delivery system, allowing for continuous, once-daily administration and better patient compliance. The transdermal formulation delivers rotigotine at a constant rate over 24 hours, providing a more continuous plasma concentration than oral formulations of dopamine agonists that are routinely administered several times a day.

The most common side effects of rotigotine include a high incidence of local reactions, nausea and somnolence. The rotigotine transdermal system is well tolerated at doses up to 6 mg/24 h. It is also useful in patients who have difficulties with oral medications because of dysphagia. The transdermal route avoids fluctuating gastrointestinal absorption due to delayed gastric emptying, as well as hepatic first-pass effects. If side effects occur, the patch can easily be removed, leading to accelerated termination of such effects.

Furthermore, rotigotine is metabolized renally and hepatically. The hepatic metabolism occurs via a multitude of cytochrome enzymes, thus lessening the risk of drug-drug interactions. Overnight switch to rotigotine is convenient, well tolerated, and effective for control of PD signs and symptoms for patients previously receiving low-to-moderate doses of oral dopaminergic agonists. Transdermal rotigotine also significantly improves 'off' time in patients with PD not optimally controlled with levodopa.

Ropinirole Prolonged-release Preparation

A ropinirole 24-hour prolonged-release preparation has been newly introduced into the market, and is effective in treating early PD. Switching from the previous ropinirole immediate-release formulation to the prolonged-release for-

mulation can be done overnight, and the acceptance and tolerability are good. The advantages of this preparation are once-daily dosing, faster titration, and more stable plasma levels. In addition, this preparation provides continuous delivery of ropinirole over 24 hours, resulting in a smooth plasma concentration-time profile, and food has no significant effect on absorption.¹³ This drug was found to be a good adjunct therapy in patients with PD not optimally controlled with levodopa, and can improve both motor and nonmotor PD symptoms while permitting a reduction in adjunctive levodopa dose. A similar formulation has been developed with pramipexole.¹⁴

Conclusion

Several treatment options are available to evoke continuous dopaminergic stimulation. Duodenal infusion of levodopa appears to be the most promising for achieving true constant brain dopamine level. Other alternatives are subcutaneous apomorphine, transdermal rotigotine and long-acting ropinirole or pramipexole. Newer agents are also being developed along this line of thoughts.¹⁵

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Common Misunderstandings About Bipolar Disorders



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The term ‘bipolar disorders’ is relatively new, invented in the past 10 years or so, although psychiatric disorders with extreme mood changes have been well known for decades. The most representative of what is now known as bipolar disorder was called manic depressive psychosis. This term is still used today, but the concept of bipolar disorders has changed so dramatically and rapidly that sometimes doctors are still not well acquainted, and misunderstandings about this category of disorders still persist. The following are some topics of interest that are often misunderstood by medical practitioners.

1. Bipolar Disorders are not Common in Clinical Practice

In the past, psychiatric wards were predominantly occupied by ‘schizophrenic’ patients, but in reality, a significant percentage of these ‘psychotic’ patients actually had bipolar disorders. Nowadays, acutely manic or depressed (suicidal) patients form a substantial proportion of newly admitted psychiatric patients. This

is because we have applied stricter criteria for schizophrenia or schizophreniform disorder, while the classification of bipolar disorders has widened considerably. Nevertheless, there are discussions about a continuum between bipolar disorders with schizoaffective disorder moving into schizophrenia.

In the community and in primary care in particular, bipolar disorders are not uncommon either. In a way, a patient can still be bipolar whether the mood state is high or low or even neutral (euthymic state), and if the doctor searches for past psychiatric history, many of those presenting with depression are actually having bipolar disorder. If one includes those with cyclothymia in the so-called ‘bipolar spectrum disorders’, the percentage would be higher. Studies in Hong Kong did find quite a high percentage of people suffering from bipolar disorders.^{1,2} Note that patients can have both high and low mood at relatively the same time (called mixed episodes).

One must not label persons with a psychiatric diagnosis if there is no distress to themselves or others, and if they do not suffer from any functional disability. Indeed, there are many people with a fairly labile mood who are often quite successful in society, but they do

Table 1. Bipolar spectrum disorders – Ghaemi et al criteria

<p>A. At least 1 episode of major depression</p> <p>B. No history of spontaneous hypomania/mania</p> <p>C. Either 1 or 2 below + at least 2 from D:</p> <ol style="list-style-type: none"> 1) A family history of bipolar disorder in a first-degree relative; or 2) Antidepressant-induced hypomania/mania <p>D. If none of C, at least 6 of the following:</p> <ol style="list-style-type: none"> 1) Hyperthymic personality (at baseline nondepressed state) 2) Recurrent major depression (>3 episodes) 3) Episodes of major depression are brief (<3 months on average) 4) Atypical depression symptoms 5) Psychosis during depression 6) Early age of onset of major depression (<25 years) 7) Postpartum depression 8) Antidepressant loss of response (acute but not prophylactic response) 9) Lack of response to >3 antidepressant trials
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Adapted from reference 3.

not suffer from bipolar disorder. Nevertheless, there are a few professionals, including artists and designers, actors and actresses, musicians and composers, politicians and entrepreneurs, who self-profess or have been diagnosed with bipolar disorders. One well known politician is Winston Churchill, famous Prime Minister of England.

2. Bipolar Disorder Means Manic-depressive Psychosis

Though the term can still be used interchangeably, bipolar (mood) disorder is not just mania, depression or psychosis. Very often seen in the community is hypomania rather than full-blown mania, and many of the patients are nonpsychotic. The bipolar spectrum disorders that doctors are talking about are not necessarily psychotic.³ (Table 1)

3. Bipolar Disorder is Very Similar to Unipolar Depression

Definitely there are quite a lot of similarities between bipolar and unipolar depression. (Table 2) Very often, bipolar disorder is diagnosed for patients presenting with features of unipolar depression or major depressive disorder. In patients suffering from bipolar disorder, the misdiagnosis of unipolar depression is common (41% according to a US study).⁴

There are significant differences between the two conditions. (Table 3) It is important to sense the differences when a patient presents with depression, as undue overenthusiastic prescription

Table 2. Similarities between bipolar disorder and unipolar depression

Clinical symptoms:

- Distractibility, irritability and ruminations can be symptoms of a mixed episode or unipolar depression
- High levels of activity may be either manic hyperactivity or agitated depression – for the former, it is goal directed; for the latter, it is stereotyped and purposeless

Table 3. Differences between bipolar disorder and unipolar depression

The course is quite different:

- For bipolar depression, there is earlier onset than major depressive disorder
- Postpartum depression is more likely bipolar disorder
- In bipolar disorder, duration of depression is longer than manic/hypomanic symptoms:
 - Bipolar I – 3 times longer with acute/subsyndromal depressive symptoms
 - Bipolar II – even longer duration of depressive symptoms, and more recurrent or frequent depressive episodes; symptoms more likely to begin and subside abruptly; increased chronic phase

Clinical symptoms of bipolar depression:

- More hypersomnia and hyperphagia
- More psychomotor changes
- Psychotic symptoms
- Greater extraversion and novelty-seeking tendencies
- Less judgmental on psychometric tests
- Higher risk of suicide and impaired functioning (even with subsyndromal depression)

Table 4. Similarities between bipolar disorders and schizophrenia

- Similar lifetime prevalence across all cultures in both sexes (bipolar I, 1–2%; schizophrenia, 0.7–1.2%)
- Typical early onset in late adolescence or early adulthood (rare after age of 50); affecting men and women equally
- Episodic course throughout lifespan (recurrence rate >90%) with progressive deterioration of function; spontaneous, lifelong remissions are uncommon; similar recurrence rate of >90%
- Similar comorbid substance abuse (bipolar disorders, 50–60%; schizophrenia, 20–50%) and suicide risk
- Similar symptoms (eg, depressive and psychotic features, premorbid attentional impairment, insomnia and restlessness)
- Similar response to atypical antipsychotics

Table 5. Differences between bipolar disorders and schizophrenia

Memory impairment is greater in schizophrenia than bipolar disorders:

- Bipolar patients are impaired under repetition (repeated contextual information improves the performance) and under novelty (encoding of a holistic impression of stimuli improves performance) conditions
- Schizophrenic patients have impaired organization of contextual conditions but not holistic processing

Language organization is different:

- For mania – logorrhoea, flight of ideas, maintain correct links between sentences (abnormal ventral prefrontal cortex, ventral striatum and insula, which are involved in processing of hedonic experiences)
- For schizophrenia – highly disorganized (abnormal dorsolateral prefrontal cortex, which is involved in working memory⁶)

Genetic differences:

- Though there are some shared genes between the two disorders, there are some that are unique for either
- For schizophrenia, genes such as disbindin at chromosome 6p22 are compounded by neurodevelopment impairment
- For bipolar disorders, reactivity of genes such as DAOA(G72/G30) at chromosome 13q33 and BDNF at chromosome 11p13 to social events is implicated⁷

of potent antidepressants (now relatively safe to use by doctors) may induce a hypomanic (or even a manic) swing in susceptible bipolar patients, and continued use of antidepressants alone may induce rapid cycling.

4. Bipolar Disorder is Similar to Schizophrenia

According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), bipolar disorders can be psychotic, but would be diagnosed only

if 'not better accounted for by schizoaffective disorder and not superimposed on schizophrenia, schizophreniform disorder ...'.⁵ In clinical practice, however, many doctors would diagnose schizophrenia only if not better accounted for by bipolar disorder. This means there are real similarities between the two conditions, and the antipsychotic medications used for schizophrenia are also beneficial to bipolar disorders. (Table 4) Differentiating these two disorders is important,^{6,7} as undue use of first-generation antipsychotics for bipolar disorder may hasten the clinical condition into the depressive phase, which inherently carries a higher suicide risk. (Table 5)

5. Bipolar I is a Similar but More Severe Form of Bipolar II

All along, many clinicians have considered bipolar II as a milder form of bipolar disorder as there is hypomania instead of mania, while bipolar I is considered as a condition with psychotic symptoms. Unfortunately this is not so, and there are subtle differences between the two.⁸⁻¹¹ (Table 6) Besides, both bipolar I and II can have psychotic symptoms, and treatment is usually not the same. For example, antidepressants should not be used for bipolar I disorder, while they may be used with caution for bipolar II disorder.

6. Bipolar Disorder Treatment is Simple

In the past, doctors were taught to use antipsychotics (only first generation available at that time) for mania, while antidepressants were prescribed for depression. When the patient had 'recovered' (now called euthymic state), the medications were tailed off until the next episode. For those 'rapid cyclers', lithium or another mood stabilizer would be used as prophylaxis. According to the present regime, such an approach is nearly totally erroneous. For lack of space, readers are recommended to look at the Clinical Recommendations regularly updated by the Hong Kong Society for Advancement of Bipolar Disorders.¹²

The therapeutic regime is constantly evolving as more and more novel medications are found effective for the disorder. Prolonged or lifelong treatment is indicated for bipolar I disorders as the course of bipolar disorders usually becomes chronic, the interepisode duration shortens with time (ie, more frequent relapses), and patients in euthymic state still display cognitive deficits. Besides, mood stabilizers including lithium and other anticonvulsants are found to have some neuroprotective effect.

However, atypical antipsychotics are preferred to avoid depression in-

Table 6. Differences between bipolar I and II

Phenomenology:

- Bipolar II – more depressive spells, higher suicide risks, probably better response to antidepressants, more prevalent rapid cycling
- No difference in severity of depression for bipolar I and II, but more severe manic spells for bipolar I⁹

Neuroimaging:

- Bipolar II tends to breed true, with differences on MRI scan and presence of vascular abnormalities (Raynaud's phenomenon, migraine)⁹

Course:

- More chronic, recurrent in bipolar II than bipolar I
- More frequent previous and future episodes if untreated (especially depressive), with shorter duration in bipolar II

Shorter interepisode interval and less hospitalization in bipolar II, but bipolar II patients could have been affected by antidepressant therapy^{10,11}

duction, while antidepressants should not be given as monotherapy.¹³ In a recent local retrospective case-control review, the incidence of conversion to bipolar depression was 10.7% among Chinese psychiatric outpatients newly diagnosed of unipolar depression from 1994 to 1999 who were subsequently followed up for at least 8 years. Male sex, an earlier age at presentation of depression (<37 years), family history of bipolar disorder, and use of three or more antidepressants in the first 5 years after presentation of unipolar depression were associated with bipolar switch.¹⁴

Nowadays, combination therapy (eg, an anticonvulsant mood stabilizer plus an atypical antipsychotic, and sometimes 'triple' therapy) are preferred over monotherapy.

7. Psychotherapy is not Useful for Bipolar Disorders

So far, there is no evidence-based study showing that psychotherapy per se is therapeutic for bipolar disorders, although most of the studies done were on bipolar I patients. Perhaps a percentage of bipolar II patients may benefit from psychotherapy in an early stage of the disorder.

As an adjunct, psychotherapy can be useful,¹⁵ especially when the patients are in euthymic states.¹⁶ Group psychoeducation is more cost-effective than individual therapy.¹⁷

Furthermore, family therapy should be beneficial and can improve inter-

personal and other domains of social functioning, lower expressed emotion, and improve compliance.¹⁸

Conclusion

Research into bipolar disorders is growing rapidly, probably fueled by the interests of drug companies. One should be aware of the danger of overdiagnosis and over-treatment, especially since 'creativity' may be lost when the patient's mood is 'too stable'. Nevertheless, clinicians should keep themselves updated about this revolutionized psychiatric disorder, as bipolar II can be quite prevalent in the community and among patients seen in general practice. Doctors must also be able to explore the possibility of a bipolar disorder when the patient presents initially with features of depression. Rational use of psychotropic medications is essential, and these medications should be given for an adequate period of time at an adequate dosage before switching. In case of uncertainty or doubt, consult or refer.

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Abbreviated Prescribing Information:

Presentation: Quetiapine fumarate extended-release tablet. **Indications:** Treatment of Schizophrenia & preventing relapse in stable patients on Seroquel XR. Treatment of manic episodes and major depressive episodes associated with bipolar disorder. For preventing recurrence in bipolar disorder in patient whose manic, mixed or depressive episode has responded to quetiapine treatment. **Dosage:** Adults **Schizophrenia:** Once-daily, without food (at least one hr before meal). Starting daily dose is 300 mg (Day 1) & 600 mg (Day 2). Recommended daily dose is 600 mg. Range 400-800 mg/day depending on clinical response & tolerability of patient. Same dosage is used for maintenance therapy. **Manic episodes associated with bipolar disorder:** Starting daily dose is 300 mg (Day 1) & 600 mg (Day 2) & up to 800 mg (after Day 2). Range 400-800 mg/day depending on clinical response & tolerability of patient. **Major depressive episodes associated with bipolar disorder:** Once-daily at bedtime. Starting dose is 50mg (Day 1) & 100 mg (Day 2) & 300 mg (Day 3) & 300 mg (Day 4). Recommended daily dose is 300 mg. Individual patients may benefit from a 600 mg dose. **Preventing bipolar disorder recurrence:** Use same dose as active treatment for prevention of manic, depressive or mixed episodes in bipolar disorder. Range of 300-800 mg/day depending on clinical response & tolerability of patient. **Switching from Seroquel IR:** Switch at equivalent total daily dose. Individual adjustments may be necessary. Elderly or hepatic impairment patients initially 50 mg/day increased in increments of 50 mg/day to an effective dose. Renal impaired patients: No dosage adjustment needed. **Contraindications:** Hypersensitive to the active substance or excipients of this product. Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV protease inhibitors, azole antifungal agents, erythromycin, clarithromycin and nefazodone is contraindicated. **Precautions:** Not recommended for below 18y old; increased suicide-related events; sometimes severe restlessness; increase in cardiovascular disease; Conditions predisposing to hypotension, orthostatic hypotension; extrapyramidal symptoms; cardiac tamponade, dysrhythmia, malignant syndrome; not approved in elderly patients with dementia-related psychosis; jaundice development; venous thromboembolism; galactose intolerance. **Interactions:** Centrally acting drugs; alcohol; theophylline; carbamazepine; phenytoin; benzocaine. **Undesirable effects:** Dry mouth; withdrawal symptoms; elevations in serum triglyceride levels; elevations in total cholesterol; decrease in HDL cholesterol; dizziness; somnolence; headache; leukopenia; tachycardia; vision blurred; constipation; dyspepsia; mild asthma; peripheral edema; initially; weight gain; hyperproliferative; increased appetite; extrapyramidal symptoms; Dysarthria; elevations in serum transaminases (ALT, AST); decreased neutrophil count; blood glucose increased to hypoglycaemia level; syncope; manic; abnormal dreams & nightmares and orthostatic hypotension. **Full local prescribing information is available upon request. APLHK-SXR-0310**

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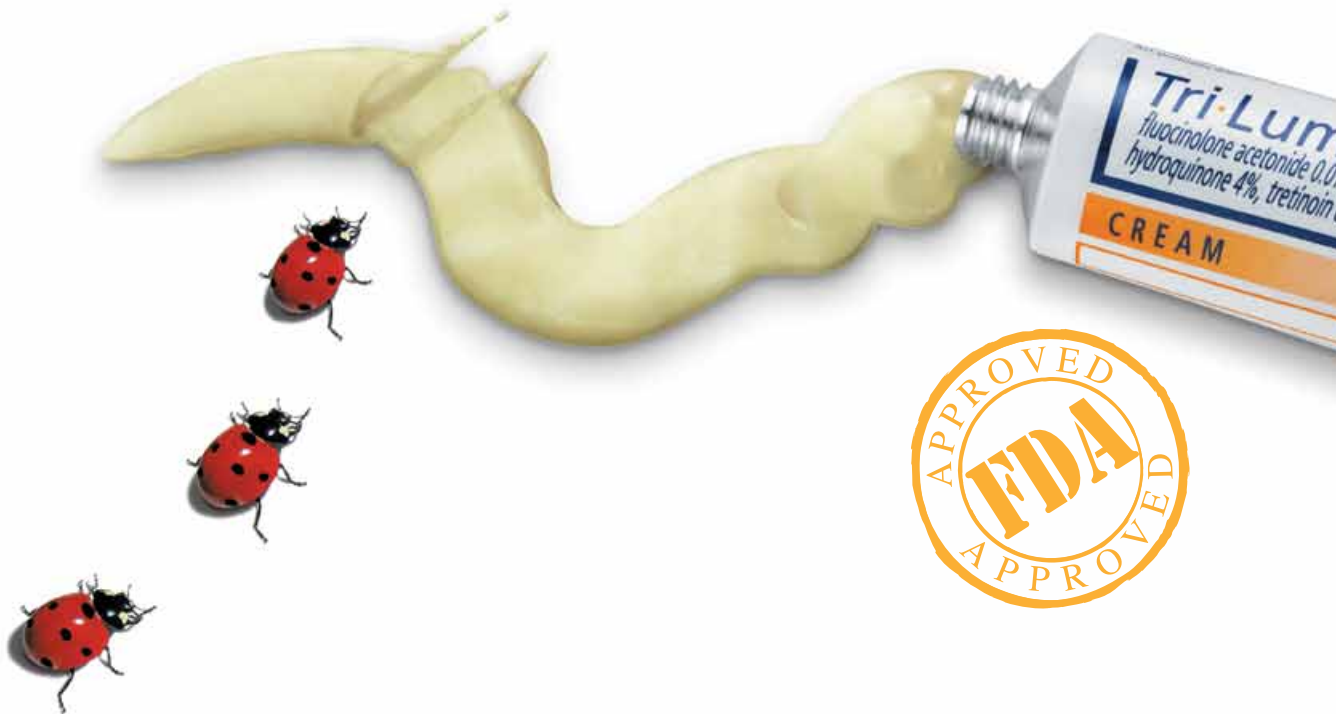
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Management of Depression by Restoring Circadian Rhythms



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Key words:

Depression (抑鬱症), circadian
rhythm (晝夜節律)

Circadian Rhythm Disturbance and Depression

Circadian rhythms are an adaptive phenomenon to the daily periodic changes in the external environment, the light-dark cycle being the most important of these. Circadian rhythms are endogenously generated and underlie a variety of biological, physiological and behavioural variables, which are characterized by their constant period of about 24 hours, amplitude and phase. The suprachiasmatic nucleus (SCN) is the site of entrainment of circadian rhythms and functions as a “biological clock” for the body. It is located in the hypothalamus and receives direct information through the retino-hypothalamic tract. An input in the form of light travels from the SCN to the paraventricular nucleus and then to the pineal gland, where melatonin (MT) is synthesized. The onset of MT release in the early evening is proven to be the most

reliable biological marker of circadian rhythms.¹ (Figure 1)

MT and serotonin (5HT)_{2C} receptors are expressed in the SCN, hippocampus and prefrontal cortex. MT₁ and MT₂ receptors are involved in the regulation of SCN activity. When stimulated, MT₁ receptors mediate the amplitude of SCN activity, while MT₂ controls phase shifting of the same activity. On the other hand, 5HT_{2C} receptors are involved in regulation of the sleep-wake rhythm. They are expressed in a circadian manner. MT receptor agonists have a beneficial effect on sleep, and antagonism at 5HT_{2C} receptors promotes slow-wave sleep.¹⁻⁴

Studies have demonstrated that depression is associated with decrease in the circadian component of diurnal mood variation. The pattern of mood observed in healthy subjects is shifted to the right (phase delay) in depressed patients; the more severe the depression, the higher this mood alteration. These findings are consistent with the hypothesis of circadian rhythm disturbances of depression and provide evidence that

Figure 1. Anatomy of the circadian rhythm system

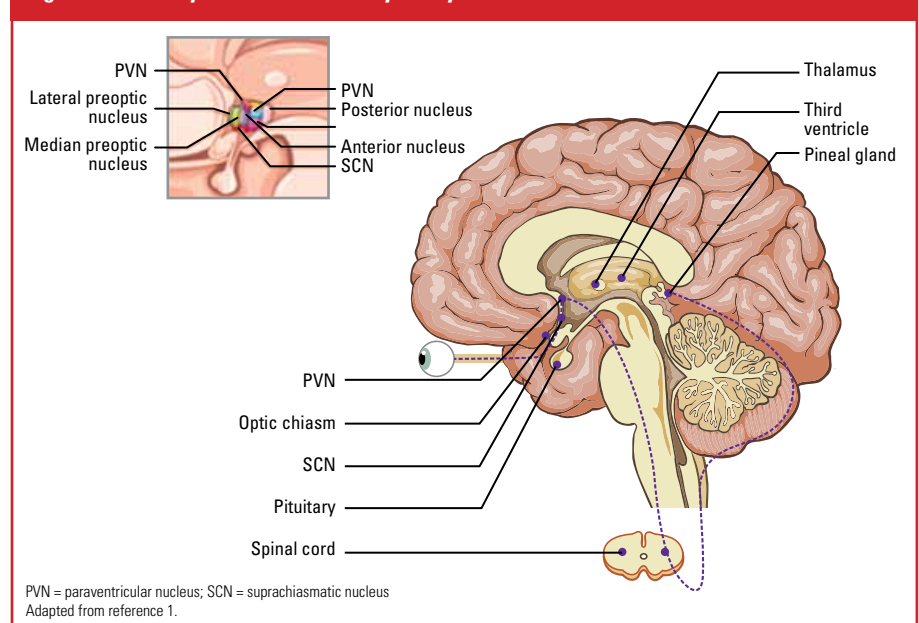


Figure 2. Receptor profile of agomelatine

Antagonist	Agonist
5HT _{2c} receptors	Melatonergic receptors
	MT ₁ IC ₅₀ 1.3 x 10 ⁻¹⁰
	MT ₂ IC ₅₀ 4.7 x 10 ⁻¹⁰
IC ₅₀ 2.7 x 10 ⁻⁷ 5HT _{2c}	

IC = inhibitory concentration; 5HT = serotonin; MT = melatonin
Adapted from references 7 and 8.

the mood variation in depression, the very core of depression, results from a weakened circadian function.^{5,6}

Management

Agomelatine is the first antidepressant with an innovative mode of action. It is an MT₁ and MT₂ receptor agonist and a 5HT_{2c} antagonist, and has no significant binding to other receptors or transporter systems. It is different from selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) as it does not have any effect on extracellular serotonin levels or downregulate the 5HT_{1A} receptor. It can restore the circadian rhythm, which is profoundly disturbed in depression, thus being efficacious in treatment of patients with major depressive disorder (MDD).^{7,8} (Figure 2)

In clinical trials, agomelatine has demonstrated superior antidepressant efficacy vs placebo and vs SSRIs and an SNRI after 6 to 8 weeks of treatment.^{9,10} It has been shown effective for a complete range of symptoms of depression, including anxiety and sleep symptoms.⁹ Significant improvement in depressive symptoms was shown at the first week of treatment compared with placebo.¹¹ In another study, depressive symptoms improved significantly more with agomelatine than with sertraline, while superior improvement of sleep latency, sleep efficiency and depressed mood was observed with agomelatine at weeks 1 and 6 vs sertraline.¹² Moreover, superior antidepressant efficacy of

agomelatine vs fluoxetine was demonstrated in severe depression at week 8.¹³ The antidepressant therapeutic advantage of agomelatine vs sertraline has been sustained in a trial up to 6 months.¹⁴ Long-term efficacy of agomelatine in terms of relapse prevention was demonstrated in a placebo-controlled trial up to 10 months.¹⁵

The tolerability and safety of agomelatine was comparable to placebo in many studies, in terms of both adverse events and laboratory parameters or specific tolerability issues, including sexual function, body weight, discontinuation symptoms, liver enzyme derangement, hormonal changes (including prolactin), blood pressure, heart rate, QTc interval, gastrointestinal upset, sedation and daytime sleepiness.^{14,16,17} Treatment adherence with agomelatine was shown to be better than with SSRIs in 6-month head-to-head comparison studies.¹⁰ In a noninterventional study conducted in Germany, agomelatine was shown to improve depressive symptoms and normalize circadian rhythms with good tolerability. As such, the clinical efficacy demonstrated in randomized controlled trials was confirmed in a real-life setting.¹⁸

Conclusion

Agomelatine improves depressive symptoms and normalizes circadian rhythms. It has been shown effective for a full range of symptoms of depression, including anxiety and sleep symptoms, and is proven to be effective in severe

depression. The efficacy of agomelatine is sustained, as shown in a relapse prevention trial. The side effect profile is good with a low risk of liver function impairment, which contributes to its good treatment adherence.

In a recent meta-analysis, the overall effect size of antidepressant drug treatment was estimated to be at 0.32 only.¹⁹ In real-life clinical practice, clinicians often encounter patients with MDD who do not respond well or do not tolerate the side effects of antidepressant medications. This is still an unresolved treatment gap in management of MDD. Agomelatine fills up this gap by providing a good option for switching from other antidepressants for efficacy and side effect reasons.

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Presentation and Composition: Each film-coated tablet contains 25 mg of agomelatine. **Indication:** Treatment of major depressive episodes in adults. **Properties:** Antidepressant. Melatonergic agonist (MT₁ and MT₂ receptors) and 5HT_{2C} antagonist. No influence on extracellular levels of serotonin. Proven antidepressant efficacy including in severe depression. Sustained antidepressant efficacy preventing relapse. Improvement of onset and quality of sleep, without daytime clumsiness from the first week of treatment. No discontinuation symptoms, or effects on sexual function, body weight, heart rate, or blood pressure. **Contraindications:** Hypersensitivity to the active substance or any excipient, hepatic impairment, concomitant use with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin). **Dosage:** The recommended dose is 25 mg once daily taken orally at bedtime. After 2 weeks, the dose may be increased to two 25 mg tablets. **Interactions:** Combination of Valdoxan and alcohol is not advisable. **Side effects:** Common: headache, dizziness, somnolence, insomnia, migraine, nausea, diarrhea, constipation, upper abdominal pain, hyperhidrosis, back pain, fatigue, anxiety, increases serum transaminases. **Precautions:** Not recommended in patients under 18 years old, pregnant women and during breast-feeding. Not for use in elderly patients with dementia. Use with caution in patients with a history of mania or hypomania and discontinue therapy if manic symptoms appear. Possible effects on the ability to drive a car or operate machinery. Perform liver function tests when initiating treatment, periodically after around 6, 12 and 24 weeks, and thereafter when clinically indicated. Perform liver function tests in patients with symptoms suggesting hepatic dysfunction. Do not use in patients with galactose intolerance or glucose-galactose malabsorption. As prescribing information may vary from country to country, please refer to the complete data sheet supplied in your country. **LES LABORATOIRES SERVIER France.** Correspondent: **SERVIER INTERNATIONAL:** 35 rue de Verdun, 92284 Suresnes Cedex, France. www.servier.com www.valdoxan.com

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Common Misunderstandings About Bipolar Disorders

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