PSYCHOTROPIC DRUGS AND SLEEP

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"Sula's dream" by Elspeth Grant.

Factors in choosing the "right" drug

- Pharmacokinetics
- Side effects: benefits
- Side effects: disadvantages
- Contraindications
- Interaction with other drugs
- History of response
- Doctor's knowledge of drug

Our aim is to summarise how some of the most commonly used psychotropic drugs may affect sleep, and we will discuss them in three groups:

- Drugs used primarily to improve sleep
- Drugs used primarily to reduce sleepiness
- Drugs used primarily to treat particular psychiatric disorders which have secondary effects on sleep

It is important that before prescribing any treatment the doctor should try to make a precise diagnosis so that he or she can decide what kind of treatment is appropriate. For example, Mr Splitman, who complains of sleep disturbance during an acute exacerbation of schizophrenia, should be given treatment different from that given to Ms Downer, whose sleep disturbance is a feature of a major depressive episode. Mr and Mrs Kryer may benefit from psychotherapy for their recent bereavement, together with a drug to relieve secondary insomnia. Mr Bullneck's hypersomnolence, irritability, and mild depression could be a secondary feature of his sleep apnoea (diagnosed by overnight electrophysiological testing), and he will probably require treatment other than drugs. In contrast, young Phil Drowse's performance at school is deteriorating, and he has withdrawn from most of his extracurricular social activities. This is, however, secondary to depressed alertness, not to depressed mood, despite apparently adequate nocturnal sleep, and suggests narcolepsy.

It is clear that drugs are only one of the treatments available for the various medicopsychiatric disorders, all of which have disturbed sleep as a common denominator. If drugs are indicated the doctor is often caught in a pharmaceutical "jungle"; choosing the right drug can be a formidable task, and the final selection depends on several factors.

Drugs used primarily to improve sleep

Benzodiazepine affinities in human brain and clinical dose.

Various hypnotic drugs that have been used in the past such as glutethimide, barbiturates, meprobamate, methaqualone, and methylprylone can be lethal; have great potential for misuse; and have no appreciable advantages over the newer compounds. For these reasons they have no place in modern treatment.

Hypnotic drugs are appropriate for the short term treatment (up to four weeks) of insomnia of recent onset caused by acute stress—for example, anxiety about examinations, or bereavement. Their use for chronic insomnia is more contentious, though they may be of benefit after the possibility of another sleep disorder has been ruled out and the causes of the insomnia have been properly investigated and treated.

Benzodiazepines have a characteristic influence on sleep architecture. They attenuate rapid eye movement (REM) and slow wave sleep, and increase stage 2 sleep. This may benefit patients whose problems are related to a particular stage of sleep such as dream anxiety attacks and night frights, but "REM rebound" occurs after treatment is discontinued, and patients may have an increase in the number of vivid or frightening dreams. In addition, tolerance to the hypnotic effects of the drugs is common after long term use.

Pharmacokinetics of some hypnotic drugs

Pharmacokinetic characteristics	Drug	Mean (SD) T _{1/2} (hours)	Dose (mg) Adult/elderly	Indications/comments
Slow absorption	Lorazepam	8	1-0-2-0/1-0	Sustains sleep; has residual daytime effects
	Oxazepam	8	15-30/10-20	Sustains sleep; has no residual effect; anxiolytic
Slow elimination	Flurazepam	64	15-30/15-0	Sustains sleep; has residual effects; anxiolytic
Slow elimination; pronounced distribution; rapid absorption	Diazepam	32	5-10/2-5-5-0	Sustains sleep; has residual effects; anxiolytic
Slow elimination; pronounced distribution	Nitrazepam	30	5-0/2-5-5-0	Sustains sleep; useful in the treatment of periodic movements
Intermediate elimination; pronounced distribution	Temazepam	8	10-60/10-20	Initiates sleep; has no residual effects
	Lormetazepam	9	1-2/0-5	Two formulations—one for sleep onset and one for maintenance
Rapid elimination	Zopiclone	5	3-75-7-5/3-75	Initiates sleep; no residual effects; no withdrawal effect
Extremely rapid elimination	Triazolam	3	0-125-0-25/0-125	Initiates sleep; has rebound insomnia and withdrawal effects.
	Zolpidem	2	10	Initiates sleep; has no residual effects; no withdrawal effects

Zopiclone and zolpidem are not benzodiazepines.

Some newer hypnotic compounds (for example, zopiclone and zolpidem) seem to have similar sleep enhancing properties but are less likely to alter sleep architecture, and it is claimed that patients are much less likely to develop tolerance or dependence. Zopiclone may actually increase the amount of slow wave sleep, which is particularly relevant for those patients who complain of chronic fatigue or diffuse musculoskeletal discomfort, or both, and may be associated with reduction in both the quality and the quantity of slow wave sleep.

The onset of the hypnotic effect is regulated mainly by the drug's rate of absorption, but accumulation of the drug and its potential "carry over" effects and sedation during the day are related to the elimination half life of the drug and its active metabolites. For example, triazolam resulted in little accumulation and few daytime effects, but because of its short half life patients tended to have withdrawal effects between doses, which led to wakefulness in the early morning and rebound anxiety. In contrast, flurazepam, which has a long half life, may cause sedation during the day but has no rapid withdrawal effects.

These drugs are metabolised mainly in the liver and excreted in the urine. The dose does not have to be adjusted in patients with mild or moderate hepatic disease or renal failure, but in patients with severe liver disease a sedative that is not metabolised in the liver (such as oxazepam or lorazepam) is recommended. The sedative effects of benzodiazepines can be magnified in patients with coexisting brain disease and in elderly people, and they may require a reduced dose.

Drugs used primarily to reduce sleepiness

Pharmacological effects of some psychostimulant drugs

Drug	Alerting effect	Sympathomimetic effect	Dose (mg) Adult/elderly
Dexamphetamine	++++	++++	5-60/2-5-40
Methylphenidate	++++	+++	30-60/15-30
Pemoline	++	+	37-5-75/25-50

Commonly used preparations of methylphenidate and selegiline.

The class of drugs most widely prescribed to treat excessive sleepiness during the day are those that stimulate the central nervous system. Amphetamines were the first; they were unique in their pronounced alerting effect after a single oral dose, but the common side effects (which included irritability, tachycardia, and insomnia, as well as tolerance and dependence) made methylphenidate the preferred drug. It is more rapidly absorbed and has appreciably fewer sympathomimetic side effects. Pemoline, an oxazolidone derivative, is much less effective, but is tolerated well and has a longer half life. It is generally recommended for milder forms of sleepiness for which treatment with a stimulant is required—for example, narcolepsy. We have found that high doses of selegiline hydrochloride (up to 30 mg/day) are useful for both narcolepsy and nocturnal myoclonus.

All psychostimulants have profound effects on sleep. They reduce the total duration of sleep, REM sleep, and slow wave sleep, and increase the time taken to fall asleep and the fragmentation of sleep. These drugs must be given in the recommended divided doses, the highest being given in the morning and tapering to the last at 1600 or 1700 at the latest. For example, methylphenidate can be divided as follows: 20 mg in the morning, 10 mg at 1200, and 10 mg at 1600 (if necessary). To make sure that the treatment is appropriate, and that the optimal dosage regimen has been established, a "maintenance of wakefulness" test should be done before and after treatment to find out the degree of daytime sleepiness. The patient's sleep/wake routine must also be considered, as restriction of sleep is a common cause of hypersomnolence.

Drugs for psychiatric disorders with secondary effects on sleep

Pharmacological effects of antidepressant drugs

Drug	Sedative effect	Anticholinergic effect	Dose (mg) Adult/elderly
Tricyclic (tertiary amines):			
Amitriptyline	+++++	++++	150-200/100
Trimipramine	++++	+++	150-200/100
Doxepin	++++	+++	150-250/100
Imipramine	+++	+++++	150-200/100
Clomipramine	+++++	+++++	150-200/100
Tricyclic (secondary amines):			
Nortriptyline	++	+++	75-100/100
Protriptyline	+	+++	30-40/30
Desipramine	+	+	150-250/100
Tetracyclic:			
Maprotiline	++++	++	200-250/150
Mianserin	++++	+	30-90/30
Triazolopyridine:			
Trazodone	++++	++	100-25/100
Phenylpropylamine:			
Fluoxetine	+/-	+	20-40/10

Some commonly used hypnotic and antipsychotic drugs.

Lithium carbonate is the mood stabilising drug of choice
Carbamazepine and sodium valproate are used in those who do not respond to lithium

Antidepressants

Tricyclic antidepressants and monoamine oxidase inhibitors have traditionally been used to treat depression. Recently their indications have been broadened to include panic disorders, agoraphobia, dysthymic disorders, depression in medical illness, and depression in schizophrenia.

Some antidepressant drugs have a mild alerting effect, which can be exploited in certain regimens of treatment. Mazindol, an imidazole derivative, is anorectic and has a mild stimulating effect on the central nervous system. Some other monoamine reuptake blockers such as protriptyline, voloxazine, fluoxetine, and some monoamine oxidase inhibitors, may actually improve alertness during the day, performance of psychomotor tasks, and cognitive functioning. Fluoxetine is a new antidepressant which has little if any anticholinergic activity and may increase anxiety. Surprisingly, formal sleep studies of this drug have not yet been published. Psychotropic drugs that have even mild activating effects should be taken early in the day to improve waking performance while minimising the possibility of iatrogenic insomnia.

The sedative effects of most of the cyclic antidepressants parallel their anticholinergic properties, so the tertiary amines are the most soporific and anticholinergic, and the secondary amines less so. Drugs such as amitriptyline and doxepin should be given later in the day, as agitated patients may benefit from their sedative side effects.

Antidepressant drugs cause immediate and profound effects on sleep architecture, of which pronounced suppression of REM sleep is the most important. This has been effectively exploited in non-psychiatric treatments so that symptoms associated with REM sleep, such as some apnoeas, and cataplexy in narcolepsy, may be brought under control. Clomipramine, which has the most suppressive effect on REM sleep, has been used in the treatment of recurrent severe nightmares. There are also increases in the amounts of slow wave and stage 1 sleep.

Antidepressant drugs should not, however, be used purely as hypnotics; they have similar effects so the choice of drug should take all other relevant factors into consideration.

Monoamine oxidase inhibitors have a particular niche in the treatment of atypical depression, which is characterised by "reverse" neurovegetative symptoms such as hypersomnolence and hyperphagia.

Mood stabilising drugs

Lithium carbonate is the drug of choice for the prophylaxis of bipolar affective disorders. Less rigorously documented is its efficacy in the treatment of schizoaffective disorders, borderline personality disorders, and cyclothymic personality disorders. In the management of hypomania it is usually used in combination with a neuroleptic drug. It is also used alone for depression or to augment the antidepressant effect of one of the cyclic antidepressants. Studies of the effects of lithium on sleep have shown that it reduces the amount of REM sleep and postpones its onset. The amount of slow wave sleep increases in patients with mood disorders, and in some healthy controls. Hypomanic patients may become aware of a dulling of their alertness, but this may be partly the result of resolution of their illness. Some hypomanic patients dislike the restoration of a normal sleep/wake rhythm because they lose their sense of grandiose tirelessness. If frank sedation occurs when lithium is given, toxicity should be considered (> 5 mmol/l).

Carbamazepine, which is similar in structure to the tricyclic antidepressant drugs, was first used in the 1960s to treat trigeminal neuralgia, but the indications for its use have been expanded to include various seizure disorders and the prophylaxis and acute treatment of bipolar

BMJ: first published as 10.1136/bmj.306.6888.1331 on 15 May 1993. Downloaded from <http://www.bmj.com/> on 26 April 2023 by guest. Protected by copyright.

Lithium, carbamazepine, and sodium valproate may all alter circadian rhythms

affective disorders. Although its effects are comparable with those of lithium, its use as a mood stabiliser is reserved for patients who do not respond to lithium and, perhaps, for "rapid cyclers" (patients who have four or more episodes a year) because of rare reports of agranulocytosis and aplastic anaemia.

In healthy volunteers carbamazepine augments slow wave, and suppresses REM, sleep. Drowsiness is common at the start of treatment or when the dose is increased, but is nearly always transient.

Sodium valproate is usually used to treat epilepsy but is also useful in rapid cycling bipolar affective disorders that are refractory to other treatments such as lithium. It has fewer sedative side effects than carbamazepine, and sleep architecture is altered only slightly in healthy controls; the only appreciable long term effects are increases in the duration and depth of sleep, and a reduction in the time that it takes to get to sleep.

Some pharmacological properties of antipsychotic drugs

Clinical potency (least to most)	Sedation effects	Parkinsonian effects	Anticholinergic effects	Oral dose equivalent (mg)
Thioridazine	++++	+	+++++	100
Chlorpromazine	+++++	++	++++	100
Loxapine	+++	+++	++	10
Molindone	+	+++	++	10
Perphenazine	+++	++++	++	10
Trifluoperazine	+	++++	++	5
Thiothixene	++	++++	++	5
Fluphenazine	++	+++++	++	4
Haloperidol	++	+++++	+	4

Conclusion

The cautious and considered use of hypnotic drugs (combined with behavioural modification) is an important part of the treatment of insomnia. The judicious use of stimulants in clearly diagnosed hypersomnolent patients is desirable.

because they feel less in control, and these patients do best when given strong antipsychotic drugs.

These drugs do not have particular characteristic effects on sleep, but most tend to reduce periods of wakefulness and increase the duration of slow wave sleep when they are given in therapeutic doses. The amount of REM sleep can be increased or reduced, depending on the dose. There is a pronounced reduction in the duration of both REM sleep and overall sleep when the drugs are stopped.

We thank Dr Alan M Jackson for taking the photographs. "Sula's dream" by Elspeth Grant is reproduced by permission of the artist. The figure of benzodiazepine affinities is based on data from Dr Elliott Richelson, Mayo Clinic, Jacksonville, and is reproduced with permission.

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The ABC of Sleep Disorders has been edited by Professor Shapiro.

CHRISTMAS COMPETITION WINNER

Last year the *BMJ* asked for an explanation for a most peculiar message. "A £10 note obtained from a building society in Durham had a message written on it in block letters: "This is *not* meant to buy condoms with either mum, they don't work!" Dr Michael Launer, a consultant psychiatrist in Burnley, sent the following explanation.

Manfred Ulf Malmquist (MUM for short) is the coded assumed name of one of the most ingenious drug couriers on the continent of Europe. He was, in his earlier life, an NHS surgeon who became so disillusioned with the managerial restrictions on his professional activities that he emigrated to Sweden and set up an ecstasy factory.

He devised a system of implanting hoards of the tablets, protected by a condom, in the appendix of the courier and the courier was then admitted to a prearranged private

clinic for an emergency appendectomy to retrieve the booty.

Sadly, on the ferry from Gothenburg to Newcastle one of the couriers developed true appendicitis and as a result he was taken by helicopter from the ship to an NHS casualty department in Durham, as all the other facilities in the area had been rationalised.

Having nothing else to write on in an emergency before he became comatose, he used one of the £10 notes from the wad that had been his payroll in an attempt to warn his master, MUM.

Unfortunately, the infection and subsequent peritonitis caused the courier to die from toxic shock, and in the absence of a true identity and any next of kin his assets were seized and the money was deposited in a Durham building society awaiting bids, in line with government policy to redistribute drug money to agencies that are fighting drug abuse.