NON-PSYCHOTROPIC DRUGS AND SLEEP

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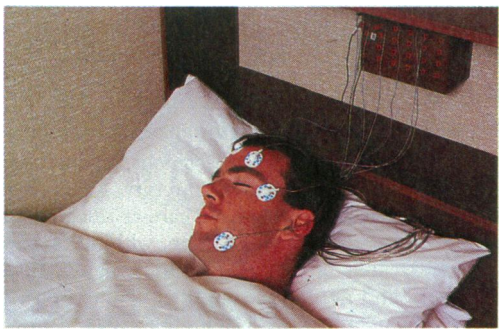

Assessment of sleep patterns.

Psychotropic drugs—drugs that affect the mental state—can also have peripheral effects. Similarly, drugs that are usually thought to have only peripheral actions may also influence the mental state, usually by affecting sleep patterns.

The mechanisms are varied. Some drugs penetrate the blood/brain barrier and directly affect the central nervous system (for example, antihistamines with sedative effects). Some drugs cause or aggravate conditions that disturb sleep—for example, sleep apnoea and restless legs. The effect may be extreme, as when sleep is broken by periods of wakefulness, or it may be subtle, as when only the electroencephalographic stages of sleep are disturbed.

General effects

"A Midsummer Night's Dream" by W Heath Robinson.

The pharmacokinetic profile of any drug is important. Those with short half lives that are taken in the morning are unlikely to affect sleep the following night. It is also unlikely that they will accumulate (unless they have metabolites with long half lives) and affect sleep in that way. Those with long half lives that are given over long periods, however, will accumulate and produce high concentrations of the drug in the body.

To understand the effects of non-psychotropic drugs on sleep we must know:

- Whether the drug is likely to enter the central nervous system: its lipophilicity will indicate whether it will enter the brain, and so whether it will affect sleep.
- The receptor binding profile, which may predict the pharmacological action, particularly if it affects one of the main neurotransmitter systems (aminergic, cholinergic, or γ aminobutyric acid). Drugs that stimulate the noradrenergic system may disrupt sleep, and those that stimulate the cholinergic system may accelerate the onset of rapid eye movement (REM) sleep, and increase the amount of dreaming.
- Whether the drug has any peripheral effects that may impair ability to sleep. For example, drugs that cause or exacerbate the sleep apnoea/hypopnoea syndrome may disturb sleep (for example, benzodiazepines), but patients may not be aware of this and subsequently complain of daytime sleepiness. Drugs that alleviate pain may have the secondary effect of improving the quality of sleep.

When a patient presents with daytime sleepiness it may be either the direct effect of the drug, or a consequence of disturbed sleep at night.

Appetite suppressants

Appetite suppressants cause both daytime sedation and disturbed sleep

Most appetite suppressants disturb sleep because they stimulate the central transmission of catecholamines. Amphetamine has the greatest effect but diethylpropion, mazindol, and phentermine also cause insomnia. Fenfluramine is the exception: it is chemically related to amphetamine, but its pharmacological action is primarily serotonergic. It releases serotonin from presynaptic sites and prevents it being taken up again; it causes both daytime sedation and disturbed sleep (by replacing sleep with periods of drowsiness and wakefulness); and it reduces the duration of REM sleep. It may increase the amount of slow wave sleep, but that may be as a consequence of disturbed sleep on the previous night.

Antiemetic drugs

Most antiemetic drugs penetrate the blood/brain barrier and probably sedate by their actions on the dopaminergic, histaminergic, or cholinergic neurotransmitter systems.

Most antiemetic drugs cause sedation. Domperidone is a possible exception

Hyoscine is a short acting, but powerful, central and peripheral antimuscarinic agent. It not only sedates, but also (by its action on the cholinergic system) reduces the amount of REM sleep and increases light (stage 2) sleep and body movements. REM sleep is increased on withdrawal of the drug.

Domperidone, which acts on the chemoreceptor trigger zone outside the blood/brain barrier, is a possible exception. Prochlorperazine, perphenazine, trifluorperazine, and thiethylperazine may all cause sedation.

Antihistamines

Histamine is a neurotransmitter that plays a part in the regulation of sleep and wakefulness, so drugs that affect histamine transmission and enter the central nervous system will affect sleep. Many of the early antihistamines also had serotonergic, noradrenergic, and cholinergic activity and entered the central nervous system.

New antihistamines have been developed that do not cause drowsiness

Examples
Astemizole
Terfenadine
Loratidine

H_1 antagonists—The older antihistamines (such as triprolidine and promethazine) invariably caused daytime sleepiness. This has led to the development of drugs that do not cause sedation (such as astemizole, terfenadine, and loratadine); these drugs either do not penetrate the central nervous system, or enter it slowly, and they do not affect other neurotransmitter systems except in high doses. Cyproheptadine is a serotonin antagonist, and both increases the duration of slow wave sleep and reduces REM sleep.

H_2 antagonists—Cimetidine increases the duration of slow wave sleep, but ranitidine does not.

Corticosteroids

The psychostimulant effects of glucocorticosteroids vary depending on the dose, the duration of treatment, and the reaction of the patient. Large doses can cause changes in behaviour and personality that range from nervousness, insomnia, euphoria, and mood swings to psychotic episodes that include both manic and depressive states, paranoia, and acute toxic psychoses. It is possible that these reactions are triggered by sleep disruption. The effects are most pronounced with dexamethasone and least with 6-methylprednisolone and prednylidene.

Large doses of steroids can cause changes in behaviour and personality

Cardiovascular drugs

Antihypertensive drugs increase the duration of REM sleep

Clonidine disturbs sleep patterns

β Blockers have a varying effect on sleep, depending primarily on their lipophilicity—more water soluble drugs are less likely to enter the brain and have an effect on sleep

Antihypertensive drugs

α Methyldopa inhibits aromatic L-amino-decarboxylase, which plays a part in the synthesis of noradrenaline and serotonin. It increases the duration of REM sleep during the first half of the night at the same time as reducing the amount of slow wave sleep, and can cause both sedation and nightmares. Reserpine blocks the synthesis of amines in the brain and depletes stores of serotonin and catecholamines. It increases REM sleep and can cause depression, drowsiness, lethargy, and nightmares.

Adrenoceptor drugs

α *Agonists*—Clonidine is associated with insomnia and vivid dreams, particularly at the start of treatment, but in the laboratory it seems to suppress REM sleep and increase the duration of slow wave sleep. Children whose mothers were treated with clonidine during pregnancy have more disturbed sleep than those who were not.

α *Antagonists*—Indoramin and prazosin may both cause transient sedation at the start of treatment. Yohimbine increases the duration of REM sleep and reduces the duration of slow wave sleep; it is also alleged to have aphrodisiac properties, but there are no data to confirm this. It is not licensed in the United Kingdom.

β *Agonists*—Salbutamol (in a dose of 1·5 mg) has been investigated in a sleep laboratory but had no effect on sleep; pseudoephedrine on the other hand does disrupt sleep.

β *Antagonists*—The incidence of sleep disturbance depends primarily on the lipophilicity of the drug concerned, but partial agonist activity, membrane stabilisation, intrinsic sympathomimetic activity, stereospecificity, and affinity for other receptors may all affect the degree of sleep disturbance and daytime drowsiness. Propranolol, pindolol, and metoprolol all disturb sleep, though few effects have been noted with solatol. Acebutolol, alprenolol, atenolol, and oxprenolol all affect sleep, but simply switching from one β blocker to another may reduce the incidence of insomnia and increase compliance.

Propranolol blocks both β_1 and β_2 adrenoceptors; laboratory studies do not show any profound effects on sleep, though there is a reduction in the amount of REM sleep. It is, however, associated clinically with disturbed sleep and nightmares.

β *Blocker*	*Partition coefficient*
More water soluble	
Atenolol	0·02
Solatol	0·04
Nadolol	0·07
Acebutolol	0·7
Metoprolol	1·0
Pindolol	0·8
Timolol	1·2
Oxprenolol	2·3
Labetalol	11·5
Propranolol	20·2
More lipid soluble	

The more lipid soluble the drug the more likely it is to cause insomnia and nightmares

Partition coefficients of lipid solubilities of various β blockers. The more lipid soluble they are, the more likely to cause insomnia and nightmares.

Diuretic drugs

Acetazolamide promotes a bicarbonate diuresis with consequent lowering of the pH value. It has been used prophylactically for acute mountain sickness and may be useful for central apnoea. Spironolactone may cause drowsiness. The timing of the dose of diuretic may cause disruption of sleep because of the need to pass urine during the night.

Hormones and vitamin A

Sleep disturbances caused by hypothyroidism resolve when the condition is treated

Sex hormones—An unusual complication of androgens (and of anabolic steroids) is the obstructive sleep apnoea syndrome, particularly with nandrolone.

Human growth hormone—Most human growth hormone is released at night, so treatment with it is best given in the morning—the optimum point in the circadian cycle.

Thyroid hormones—Hypothyroidism is associated with little or no slow wave sleep and disturbed REM sleep. Sleep is restored to normal when the condition is treated.

Vitamin A—Acute poisoning with vitamin A (retinol) causes symptoms of drowsiness, sluggishness, irritability, and an irresistible desire to sleep.

Herbs

Herbs, including rosemary and camomile, that are known to have sedative properties.

Almonds, camomile, catmint, fennel, ginseng, hops, indian hemp, lettuce, lime, marjoram, may blossom, melissa, mullein, oats, orange blossom, passion flower, poppy seed, rosemary, willow, and valerian are all traditionally thought to be sedatives. Most have not been investigated apart from heroin and the cannabinoids, but in some studies valerian has been found to improve the quality of sleep subjectively.

Conclusion

Many drugs alter sleep architecture. These effects may be beneficial, but may alter compliance with the primary treatment, particularly if a drug (for example, fluoxetine) causes insomnia in a person with a condition (depression) in which disruption of sleep is poorly tolerated. In this example the side effect of the drug may perpetuate the primary illness.

Awareness of the effects of drugs on sleep may lead to more appropriate prescribing

We thank Dr Alan M Jackson for taking the photographs of herbs. The previously unpublished watercolour of almond blossom was painted during the early 1920s and is reproduced with permission. "A Midsummer Night's Dream" is published by permission of the Mary Evans Picture Library.

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

OBITUARY

T S Eimerl

T S EIMERL

DSC, VRD, MD, FRCGP

Always interested in what doctors do and why, from my base in general practice I began operational research studies observing and recording trends in the patterns of work in general practice. Subsequently I became a part time member of the Health Care Research Unit at Manchester University. This was the first appointment of its kind in England, with university funds paying for a part time locum for me while I worked as adviser in general practice to the unit. In 1958 I first demonstrated the E-book, a disease index I had developed for general practice, which later became internationally known. My studies, in Britain and abroad, of general practitioners and their means of working led to many invitations to speak overseas.

I wrote widely on various aspects of my work. Possibly my most useful contribution was in 1965, when I was secretary of the working party of the College of General Practitioners that produced *Present State and Future Needs of General Practice* (described in an editorial in the *Times* as a watershed in the public and professional regard of the college). In 1969 A J Laidlaw and I edited *A Handbook for Research in General Practice*. Both publications used information from within general practice not earlier recognised to exist.

The other love of my professional life was the navy: after demobilisation I continued in the Royal Naval Volunteer Reserve, becoming principal medical officer to HMS *Eaglet* and retiring with the rank of surgeon captain.

Teviot Selwyn Eimerl, latterly a senior medical officer in the Department of Health and Social Security until 1976, died 27 January aged 76. Born Chester; studied medicine at Liverpool University (MB, ChB 1939). Served in Royal Naval Volunteer Reserve in Norway and Europe. General practitioner in Warrington for many years from 1947. Member of council of College of General Practitioners, chairman of college's research committee, and provost of its South East Thames faculty. Survived by wife, Guyda; daughter, Ann; son, David; and grandchildren.

Obituaries must be submitted exclusively to the BMJ; they should be under 250 words and submitted within three months of the person's death. We welcome self written obituaries and good quality, recent photographs, and, as a medical journal, we encourage authors to include the cause of death.

G W AYRES

MB, BS

Geoffrey William Ayres went to Chippenham in 1929 as a locum but after a fortnight's work was offered a partnership. He was senior partner of the practice for 25 years, during which time medicine in Chippenham developed around its four small hospitals. He played an active part in their administration and work, being medical officer to St Andrew's Hospital (a geriatric hospital of 190 beds) and the local isolation hospital and on the staff of Chippenham and District Hospital, where he used his surgical skills. In 1968 he and his five partners moved to a converted Victorian house. Last year his remaining partners invited him to open their new purpose built premises, which he did with enthusiasm.

Having played rugby football and cricket for both his school and medical school, on moving to Chippenham he became a founder member of Chippenham Rugby Football Club; he was president for 25 years until his retirement from practice. For many years he was a keen shot and secretary to the local doctors' shoot. He also enjoyed fly fishing and tennis. His first wife, Brenda, died in 1971; he is survived by a son and two daughters and by his second wife, Mary.—
A J WINTERTON

Geoffrey William Ayres, a general practitioner in Chippenham for 41 years, died 22 January aged 87. Educated Epsom College, St Mary's Hospital Medical School (LMSSA 1927; MB, BS 1928). Chairman of Trowbridge division of BMA 1954.

R M MILLEN

MD, FRCOG

Robbie Millen worked for a time in Croydon with Rufus Thomas, who was then establishing his method of spinal anaesthesia as a safe technique for caesarean section. Robbie reckoned that he administered many dozens of anaesthetics that were quietly subsumed into the grand total.

Within a short time after being appointed to Chase Farm Hospital he had established, in one of the dormitories of this semi-converted poor law children's home, an active obstetrics unit that delivered most of the babies of Enfield for the next 30 years. Robbie required the highest standard of efficiency and decorum from all grades of staff. He regarded obstetric emergencies as needing the most senior people available, so it was not unusual to meet him in the delivery room or theatre at any hour of the day or night. During the early 1950s, with an absence of publicity and complete success, he performed one of the early sex change operations.

Robbie was active in hospital affairs, in the masons, and in the BMA (he served as chairman of Enfield division). For some 15 years he was concerned in