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REVIEW

Drug induced nightmares—an etiology based review

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Objective Recent clinical trials have included patient complaints of nightmares as a category of reportable medication side effects. This study integrates that data into current experimental and theoretical research of drug effects that may alter dreaming and nightmares. The objective is to provide a clinical and theoretical framework useful in categorizing the potential and reported drug effects on nightmares.
Methodology This study reviews case reports and clinical trials that have reported nightmares or alterations in dreaming occurring secondary to medication usage. These data are analysed as to the probability of the drug/nightmare association, and integrated into current electrophysiological and neurochemical theories of dreaming and nightmares.
Results Pharmacological agents affecting the neurotransmitters norepinephrine, serotonin and dopamine are clearly associated with patient reports of nightmares. Agents affecting immunological response to infectious disease are likely to induce nightmares in some patients. A possible association exists between reports of nightmares and agents affecting the neurotransmitters acetylcholine, GABA and histamine, as well as for some anesthetics, antipsychotics and antiepileptic agents.
Conclusion By utilizing our current experimental and theoretical knowledge base, the potential etiology of a majority of reported drug effects on nightmares can be classified. These data support current neurochemical theories of dreaming, as well as suggesting that the biochemical basis for dreaming and nightmare induction may be more complex than generally suggested.

KEY WORDS — dreaming; nightmare; GABA; acetylcholine; norepinephrine; serotonin; dopamine; histamine; anesthetics

INTRODUCTION

Recent clinical trials have included patient reports of nightmares and alterations in dreaming. When integrated with case reports over this same period of medications noted to induce nightmares, an emerging pattern of medication classes noted to induce nightmares becomes apparent. These data support current neurochemical theories of dream alteration based on neuroreceptor modulation in the central nervous system (CNS), but also suggests that groups of medications other than those classically described to induce nightmares are also associated with clinical reports of disordered dreaming. Analysis of these data provide a framework that can be used both clinically and in research to identify pharmacological agents and biochemical pathways likely to affect dreaming and nightmares.

DEFINING THE NIGHTMARE

The DSM-IV defines a nightmare as a frightening dream, avoiding the confusing question of the general use and research definition of dream (Francis, 1994). The terminology—anxiety dream and dream anxiety attack—in general use is interchangeable with nightmare. This approach is incorporated into some studies while in others an anxiety dream is defined to be a different area of frightening dream classification Krakow and Neidhardt, 1992). There is no generally accepted

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definition for dream, however, dream definitions can be categorized (Pagel *et al*., 1999, 2001). Definitions for dreaming should include nodal definition points from three axes: (1) sleep/waking, (2) recall and (3) content. Clinically the most commonly used definition for nightmare comes from the American Academy of Sleep Medicine (AASM), 'an unpleasant or frightening dream usually occurring in REM sleep' (Thorpy, 1997).

The pharmacological literature has generally addressed dreaming by quantifying its physiological correlates, especially REM sleep. Psychoactive medications alter the EEG associated with sleep, often affecting REMS percentage, latency, associated phasic activity and the amplitude and frequency of sleep associated EEG rhythms (Pagel, 1993, 1996). One of the major factors affecting dream recall is the sleep stage from which the dream is elicited. Dream recall is highest on awakenings from sleep onset and REM sleep (>80%) (Foulkes, 1985). Recall from other non-REM stages of sleep depends primarily on the stage's distance from awake, being lowest from deep sleep (approximately 40% of awakenings associated with dream recall). One variable affecting dream recall is dream content. Dream salience—the greater novelty, bizarreness, affectiveness or intensity of an experience may increase the potential for recall of a particular dream (Cohen, 1979). Dream salience characterizes the nightmare, which is most likely to be associated with REM sleep. The dream remembered in the morning is most likely to be from the longest, and most physiologically disturbed REMS period (most eye movements and irregularity of respiration) (Baekeland and Lasky, 1968; Mellman *et al*., 1995). The association of dreaming with particular sleep states appears, however, to be doubly dissociable with dreaming occurring outside REM sleep and REM sleep occurring without dreaming (Foulkes, 1985; Solms, 1997).

NIGHTMARE INCIDENCE

Studies of nightmare have been limited by incidence frequency and the lack of specificity of the complaint. The complaint is common, with nightmares reported as occurring on a frequent basis by more than 50% of the individuals in some populations (Pagel, 2000). Some 5% to 8% of the general population report a current problem with nightmares (Bixler *et al*., 1979; Klink and Quan, 1987). In a general population study of 1049 patients with insomnia, 47% reported having at least one nightmare/week (Moffitt *et al*., 1993). In this study nightmares were more common in women and were associated with increases in nocturnal awakenings, sleep onset insomnia and daytime memory impairment and anxiety following poor sleep. Nightmares affect from 20% to 39% of children between 5 and 12 years of age (Terr, 1987). In a 2-week prospective study of college students, 47% described at least one nightmare (Wood and Bootzin, 1990). Frequent nightmares are the most common symptom of post-traumatic stress disorder (PTSD) (Fawzi *et al*., 1997). The nightmares of PTSD are often associated with disturbed sleep and altered daytime behavior that is best described as hyperarousability (Grillon *et al*., 1996). The incidence of PTSD following trauma varies at least in part based on the severity of trauma. Thirty percent of Vietnam war veterans were affected by PTSD, as were 68% of veterans of the 1973 Arab–Israeli conflict and 8% of veterans of the Gulf war (Yehuda and McFarlane, 1995). Among the civilian population PTSD affects approximately 25% of individuals experiencing severe emotional or physical trauma or a severe medical illness (Schenck and Mahowald, 1996). In some groups of patients (i.e. immigrant psychiatric patients) the incidence of PTSD exceeds 40% (Ekblad and Roth, 1997). The nightmares of PTSD generally happen during REM sleep but also occur at sleep onset (stages 1 and 2) interfering with the initiation of sleep (Ross *et al*., 1989).

NEUROTRANSMITTER MODULATING SYSTEMS POSTULATED TO BE INVOLVED IN DREAMING AND NIGHTMARES

Acetylcholine

REM sleep is affected by pharmacological alteration of cholinergic activity in the CNS (McCarley, 1982). Many lines of study support the hypothesis that brainstem cholinergic neurons can be excited to induce REM sleep (Hobson, 1994; Jouvet, 1999). Cholinergic agents are most likely to increase the percentage of REM sleep, with cholinergic antagonists tending to decrease REM sleep (Hobson and Steriade, 1986). Some of the most commonly reported side effects of agents with anticholinergic activity include nightmares, disordered dreaming and hallucinations. A wide variety of pharmaceutical agents have anticholinergic activity. The cholinergic activity of these agents has been postulated to explain the CNS side effects, including nightmares and hallucinations, of these drugs (Perry and Perry, 1995).

Norepinephrine

Antihypertensive agents in general use affect adrenergic CNS receptors. These drugs have been shown to

affect both REM sleep and reports of dreaming. The reported effects of these agents on both dreams and nightmares is often opposite to the drug's known pharmacological effects on REM sleep (Dimsdale and Newton, 1991). Decreases in dream recall occur with the use of both alpha agonists (REM suppressant) and beta blockers (non-REM suppressant). An agent's effect on REM sleep may or may not be associated with an associated change in reported dreaming. The use of beta-blockers depresses REM sleep percentages, yet can result in reports of increased dreaming, nightmares and hallucinations (Brismar *et al*., 1987).

Serotonin

Antidepressants affecting serotonin metabolism often induce REM sleep suppression. This effect is greatest for the monoamine oxidase inhibitors (MAOIs) followed by the tricyclic antidepressants and the selective serotonin reuptake inhibitors (SSRIs). REM sleep suppression is not generally seen with buspiron, trimpramine and nefazodone (Gursky and Krahn, 2000). Intense visual dreaming and nightmares are associated with clomiprimine, paroxetine and fluvoxamine withdrawal (Coupland *et al*., 1996). This effect could occur secondary to REM sleep rebound occurring after the withdrawal of these REM sleep suppressant agents, but studies of reported dream recall with antidepressant use show that recall may vary independently of REMS suppression, though an initial decline in dream recall may occur during the period of initial dosing of the agents (Pace-Schott *et al*., 1999). Studies of chronic steady state use and antidepressant withdrawal have shown inconsistent effects: increased dream recall with SSRIs and tricyclic antidepressants, no effect, and decreased recall (Lepkifker *et al*., 1995; Pace-Schott *et al*., 2000).

Dopamine

Dopamine receptor stimulation may be another common mechanism resulting in drug induced nightmares. Medications efficacious in the treatment of Parkinson's disease share the tendency to cause disordered dreaming. Dopamine, bromocriptine, pergoline and other dopamine agonists can lead to vivid dreaming, nightmares and night terrors which can be the first signs of the development of drug induced psychosis (Stacy, 1999). While amphetamines are adrenergic agonist agents, cognitive side effects such as nightmares have been postulated to occur secondary to dopamine receptor stimulation (Thompson and Pierce, 1999).

GABA

Nightmares and intense dreaming have been associated with the REM sleep rebound associated with withdrawal from REM sleep suppressing agents. In addition to antidepressant agents, REM sleep suppressants include: ethanol, barbiturates, benzodiazepines, non-benzodiazepine hypnotics and sympathomimetic drugs (Pagel, 1993, 1996). Several authors have suggested that the nightmare inducing characteristics of these agents reflect the drug effects at the GABA receptor (Pace-Schott, 2000; Xi *et al*., 1999; Mallick *et al*., 2001).

Other agents with a reported association to nightmare induction

The literature describing drug effects on dreaming consist primarily of reports of vivid dreaming/nightmares as a side effect of medication or as a symptom of medication withdrawal. The high frequency of nightmares in both general and psychiatric populations makes interpretation of drug induced nightmare data difficult since few of these studies include blinded or placebo cohorts for comparison. Historically, several groupings of medication types have been associated with nightmare occurrence secondary either to withdrawal, toxicity or as side effects of use (Table 1).

Much of the literature concerning pharmacological agents reported to induce nightmares is related to agents used in anesthesia. Although not clearly sleep, some induction anesthetics are reported to cause altered dreaming. An increased incidence of 'pleasant' dreams are reported with profolol use (Oxorn *et al*., 1997). Both the barbiturate thiopental, isoflurane and ketamine have been reported to produce disordered dreaming and nightmares (Knill *et al*., 1990; Marsh *et al*., 1992; Krissel *et al*., 1994). Ketamine can induce waking hallucinations and confusion. This association has, in part, led to proposals that dreams and nightmares are hallucinatory experiences occurring during sleep (Hobson, 1999).

METHODOLOGY

This study is a review of case reports (CR) and clinical trials (CT) of medications in clinical use in the United States reported to induce nightmares and alterations in dreaming (Thompson and Pierce, 1999; Sifton, 2002). A qualitative probability assessment is used to determine the probability that nightmares are drug induced by these agents based on the Naranjo (1981) algorithm

Table 1. Medication types known historically to cause nightmares

Drug classes known to induce nightmares	Type of effect	Postulated pharmacologic etiology for nightmare induction
Amphetamines and amphetamine like agents	Associated with chronic use and withdrawal	Noradrenergic/dopaminergic
Anticholinergics	Associated with chronic use and toxicity	Cholinergic
Barbiturates and barbiturate-like agents	Known side effect on withdrawal	REM rebound
Benzodiazepines	Known side effect on withdrawal	REM rebound/GABA
Dopamine agonists	Associated with chronic use and over-dosage	Dopaminergic
Ethanol	Known side effect on withdrawal	REM rebound
Hallucinogenics	Toxicity and effect of use	Serotonin and norepinephrine, cognitive effects, cholinergic
Tricyclic antidepressants	Drug and withdrawal effects	Serotonin and norepinephrine

ranging from definite–probable–possible–doubtful (Naranjo *et al*., 1981). The association between each medication and described side effect (nightmares or alterations in dreaming) in clinical trial reports is rated from significant ($p < 0.01$), to probable (reported by $>1\%$ of population relative to controls), to possible (less than 1% difference compared with control or in studies without controls) to doubtful (minimal evidence for side-effect/drug association). The basis for these determinations is included in each tabular report (Tables 2 and 3). Central nervous system (CNS) active agents often affect multiple neuroreceptor systems making the classification of pharmacological affects sometimes difficult. In this study of agents routinely utilized in clinical practice, drugs are classified according to their primary clinically utilized pharmacological effect. These data are integrated into existing neurochemical theories of dreaming and nightmare induction.

This study does not include data concerning drugs for which no effects on dreaming or nightmares are reported, because of concerns as to the significance of negative reports. Older (before 1990) clinical trial data must be reviewed with some caution since clinical trial reports for agents known to induce nightmares (examples: tricyclic antidepressants, amphetamines and benzodiazepines [Table 1]) often do not include reports of nightmares or disturbed dreaming. These clinical trials are likely not to have included queries for altered dreaming or nightmares. Some newer agents of similar pharmacological types (examples newer amphetamine preparations) achieve formulary status by using data from older clinical trials. Clinical trials for agents without known psycho-pharmacological effects may also not include queries as to whether alteration in dreaming occurs. Nevertheless, this study describes a large number of newer and diverse pharmacological agents reported to induce nightmares in clinical trials (Tables 2 and 3).

DATA AND RESULTS

Case reports and clinical trial reports of agents affecting neurotransmitters reported to induce nightmares

Acetylcholine. Several lines of experimental evidence demonstrate a primary role for acetylcholine in the induction of REM sleep (Hobson and Steriade, 1986; Hobson, 1994; Perry and Perry, 1995; Jouvet, 1999). It was expected that pharmacological agents affecting acetylcholine metabolism would have been reported in case reports and clinical trials to induce nightmares. Several acetylcholinesterase inhibitors (donepezil, rivastigmine and tacrine) act as cholinergic agonists and are rated as possibly associated with reports of disordered dreaming based on clinical trial data (Table 2).

Norepinephrine. Beta-blocker and alpha-agonist agents are responsible for 34% of clinical trials in which nightmares are reported as an adverse effect (Thompson and Pierce, 1999). In this study beta-blockers were the agents most commonly associated with patient reports of nightmares. The association was considered probable for atenolol, betaxolol bisopropolol, labetolol, oxprenolol and propranolol. The adrenergic agonist guanethidine and the rauwolfia alkaloid, deserpidine, have a probable association with nightmare reports (Table 2).

Serotonin. Case reports of nightmares are associated with fluoxetine and other antidepressants (Lepkifker

Table 2. Medications affecting CNS neurotransmitter systems reported to induce nightmares in clinical trials and case studies

Affected neuroreceptor Drug	Patient reports of nightmares—evidence base clinical trials (CT) case reports (CR)	Probability assesment of drug effect
—Acetylcholine—Cholinergic agonists		
Donepezil	CT [3/747 report disordered dreaming]	Possible
Rivastigmine	CT [1/100-1/1000 report disordered dreaming]	Possible
Tacrine	CT [1/100-1/1000 (2076) report disordered dreaming]	Possible
—Norepinephine—beta blockers		
Atenolol	CT [3/20 patients]	Probable
Betaxolol and carbachol [opth.]	CR [1]—de-challenge	Possible
Bisopropol	CT [3/68 patients]: CR [1]—de-challenge	Probable
Labetalol	CT [5/175 patients]	Probable
Oxprenolol	CT [11/130 patients]	Probable
Propranolol	CT [8/107 patients]	Probable
—Norepinephine effecting agents		
Deserpidine	CT—disordered dreaming listed as side effect	Possible
Guanethidine	CT [4/48 patients]	Probable
Methyl dopa	CT [infrequent reports of nightmares]	Possible
Tramadol	CR [1]—de-challenge	Possible
—Serotonin—SSRI		
Fluoxetine	CT [1–5%—greater frequency in OCD and bulemic trials: CR [4]—de and re-challenge	Probable
Escitalopram oxylate	CT [Abnormal dreaming—1% 999 patients]	Probable
Nefazodone	CT [3% (372) versus 2%control]	Probable
Paroxetine	CT [4% (392) versus 1% control]	Significant
Sertraline	CT [1/100-1/1000]	Possible
—Agents effecting serotonin and norepinephrine		
Protriptyline	CT—nightmares listed as side effect	Possible
Trazadone	CR [reports abnormal dreams]	Doubtful
Risperidone	CT [1% increased dream activity—2607 patients]	Probable
Venlafaxine	CT [4% (1033) versus 3% control]	Probable
—Dopamine—agonists		
Amantadine	CT [5% report abnormal dreams]: CR [1]	Probable[a]
Bupropion	CR [1]—de-challenge	Possible
Cabergoline	CT [1/188 patients]: CR [1]—de-challenge	Possible
Levodopa	CT [2/9 patients]	Probable
Pergolide	CT [2.7% (189) report abnormal dreams versus 4.5% placebo]	Doubtful
Ropinirole	CT [3% (208) report abnormal dreaming versus 2% placebo]	Probable
Selegiline	CT [2/49 reporting vivid dreams]	Probable
—Amphetamine like agents		
Bethanidine	CT [2/44 patients]	Probable
Fenfluramine	CT [7/28 patients]: CR [1] de and re-challenge	Probable
Phenmetrazine	CT [3/81 patients]	Probable
—GABA		
Flunitrazepam	CT [1/127 patients]	Possible
Gabapentin	CT [1/100-1/1000 (2074) report abnormal dreams]	Possible
Gaba hydroxy buterate	CT [nightmares >1% 473 patients]	Probable
Nitrazepam	CR [2]	Possible
Triazolam	CT [7/21 patients]	Probable
Tiagabine	CT [3/2531 patients]	Possible
Zopiclone	CT [3—5/83 patients]	Probable

[a]Listed under multiple drug classification.

et al., 1995). In this study SSRI use was associated with patient reports of nightmares: rated as significant for paroxetine; probable for fluoxetine, nefazodone, and possible for sertraline. Other agents that have serotonin effects are also reported to induce nightmares: probable (rintaserin), and possible (venlafaxine and zonisamide).

Dopamine. In this study a probable association with reports of nightmares was noted for amantadine, levodopa, ropinirole and selegiline. A possible association exists for cabergoline. The dopamine reuptake inhibitor bupropion has a possible association with nightmare reports. The association of the amphetamine-like agents fenfluramine and phenmetrazine with

Table 3. Other drug classes reported to induce nightmares in recent case reports and clinical trials

Drug class DRUG	Patient reports of nightmares clinical trials (CT) case reports (CR)—Evidence base	Probability assessment of drug effect
—Anesthetics		
Katamine	CR [1]	Possible[b]
Midazolam	CT [<1%]	Possible[b]
—Antiinfectives and immuno-suppressants		
Amantadine	CT [5% reporting abnormal dreams]: CR [1]	Probable[abc]
Ciprofloxacin	CR [1]—de-challenge	Possible
Erythromycin	CR [2]—de-challenge	Possible
Fleroxacin	CT [7/84 patients]	Probable[c]
Ganciclovir	CR [1]—de and re-challenge	Probable[bc]
Gusperimus	CT [13/36 patient]	Probable
—Anti-epileptics		
Ethosuximide	CT [reports of night terrors]	Possible[b]
Lamotrigine	CT [1/100-1/1000 report abnormal dreams]	Possible[bc]
Valproic acid	CR [1]—de-challenge	Possible[bc]
Zonisamide	CT [1/100-1/1000 report abnormal dreams]	Possible[c]
—Anti-psychotics		
Chlorpromazine	CR [1]—de-challenge	Possible[bc]
Clozapine	CT [4%]	Probable[bc]
Thiothixene	CR [3]—de-challenge	Possible[bc]
Anti-histamine		
Chlorpheniramine	CT [4/80 patients]	Probable[bc]
—ACE inhibitors		
Captopril	CR [1]	Possible[bc]
Enalapril	CT [.5-1% abnormal dreaming—2987 patients]	Probable[bc]
Losartin potassium	CT [>1% dream abnormality—858 patients]	Probable[bc]
Quinapril	CT	Probable[bc]
—Other agents—no proposed mechanism		
Buprenorphrine	CR [1]—de-challenge	Possible
Digoxin	CR [1]—de and re-challenge	Probable
Naproxen	CR [1]—de and re-challenge	Probable[bc]
Verapamil	CR [1]—de and re-challenge	Probable[c]

[a]Agents listed in multiple classes:
[b]Agents inducing daytime sedation as a side effect to use.
[c]Agents inducing insomnia as a side effect to use.

patient reports of nightmares is rated as probable based on both clinical trials and case report data.

GABA. Twenty-four percent of reports of nightmares come from benzodiazepine clinical trials (Thompson and Pierce, 1999). The newer non-benzodiazepine hypnotic (zopiclone) which is not associated at clinical dosages with REM sleep suppression or REM sleep rebound on withdrawal has been associated with the occurrence of nightmares in several clinical trials, as have newer agents affecting GABA re-uptake inhibition (Van Moffaert *et al*., 1990; Ansoms *et al*., 1991).

Case reports and clinical trial reports of other agents reported to induce nightmares

Several of the antihypertensive agents reported as probable inducers of nightmares (captopril, enalapril, losartin potassium and quinipril) are inhibitors of angiotensin I—converting enzyme (ACE). These agents can induce insomnia as a side effect to use. The CNS effects of these agents may be through neurotransmitter effects. In some patients ACE inhibitors lower plasma norepinephrine levels, and may inhibit presynaptic norepinephrine release and postsynaptic alpha adrenoreceptor activity (McEvoy, 2002). The clinical significance of this finding is not known.

In this study, several of the agents reported to induce nightmares are antibiotics: fleroxacin (probable); erythromycin and ciprofloxacin (possible association with patient reports of nightmares). Both amantadine and ganciclovir are antiviral agents considered by the authors to have a probable association with patient reports of nightmares. Gusperimus is an immunologic response suppressant that is also reported to induce nightmares (probable). These agents may induce nightmares by affecting sleep-related immunologic response to infectious disease (Table 3).

Two induction anesthetics are reported in clinical trials and case reports to induce nightmares. Ketamine and midazolam were considered to have a possible association with patient reports of nightmares. Several antiepileptics have a possible association with nightmares in both case reports and clinical trials (valproic acid, ethosuximide, zonisamide and lamotrigine). The antipsychotic clozapine has a probable association with nightmares, with other antipsychotics (chlorpromazine and thiothixene) noted to have a possible association. Most of these agents commonly produce daytime sedation and/or insomnia as a side effect to medication use (Table 3). The antihistamine chlorpheniramine utilized for allergy symptoms and to induce sleepiness is likely the most commonly used medication addressed in this review. Chlorpheniramine has a probable association with patient reports of nightmares. Table 3 also includes agents reported to cause nightmares for which no causality is postulated.

DISCUSSION

Neurotransmitter systems affecting dreaming and nightmares

This study supports the theoretical postulate that adrenergic, aminergic and dopaminergic neuronal populations having prominent roles in inducing nightmares. Reports of altered dreaming and nightmares are consistently associated with agents exerting pharmacological effects on dopamine, serotonin and norepinephrine. These neurotransmitters have been suggested to have functional roles in the production of dreams (Hobson and Steriade, 1986; Hobson, 1994). These neurotransmitters may function in a reciprocal interaction involving a wide spectrum of neurotransmitters interacting in an intricate modulation of the cardinal sleep stages—REM and non-REM sleep (Thompson and Pierce, 1999). This study demonstrates that beta-blockers affecting norepinephrine neuroreceptors are the agents most likely to result in patient complaints of nightmares. The strongest clinical evidence found in this meta-analysis for the association a drug with nightmare induction is for the SSRI paroxetine. Most agents affecting dopaminergic neuroreceptors have been reported in clinical trials to induce nightmares in some patients. Medications altering these neurotransmitter systems are likely to induce reports of nightmares and disordered dreaming for patients taking those medications.

The association of GABA and acetylcholine receptors with dreaming and nightmare alteration is less clearly supported by this study with the reported nightmare/drug association rated as possible (rather than probable or significant) for the majority of drugs evaluated. The finding that different types of drugs known to affect the GABA receptor (agonists, modulators and reuptake inhibitors) can result in patient complaints of nightmares and abnormal dreaming is suggestive that GABA may be a modulator of the neuronal populations involved in dreaming (Naranjo *et al*., 1981; Ansoms *et al*., 1991; Mallick *et al*., 2001). Acetylcholinesterase inhibitors affecting the acetylcholine neuroreceptor system result in a possible association with patient complaints of drug induced nightmares. Based on the known involvement of acetylcholine neuroreceptors with REM sleep and theoretical postulates of cholinergic triggers for dreaming, a stronger association was expected. This study does not provide good support for theoretical postulates that cholinergic neurons serve as the primary neuroreceptor system involved in dreaming and nightmares (McCarley, 1982; Hobson, 1994; Jouvet, 1999; Hobson and Steriade, 1986; Perry and Perry, 1995).

Other neurotransmitter modulators proposed to affect this system include orexin, adenosine, histamine, glycine, glutamate, nitric acid and neuropeptides (Pace-Schott, 2000). The commonly used antihistamine chlorpheniramine has been reported to induce nightmares suggesting a potential role for histamine as a modulator of dreaming. The neurochemical and pharmacological basis for clinical effect for many of the agents included in Table 3 remains poorly defined. It is possible that the induction of nightmares and altered dreaming by some of these agents is secondary to neurotransmitter effects that in the future may be better described.

Agents affecting host defence reported to induce nightmares

Aristotle and Hippocrates pointed out that an association exists between infection and sleepiness. Both viral and bacterial infections can be associated with large increases in NREM sleep (McEvoy, 2002). Such microbial-induced changes in sleep are considered part of the acute phase response, and can be induced by both muramyl peptides and endotoxins (McEvoy, 2002; Krueger and Fang, 2000). Some antibiotics (i.e. fluoroquinolones) are associated with patient reports of insomnia, and have been noted to induce nightmares (Krueger and Fang, 2000; Krueger *et al.*, 1986). The cytokines IL-1B and TNF-a, and prostaglandin E2 are known to be involved in non-REM sleep regulation (Pagel, 1986). Antibiotics, antivirals and immunosuppressant drugs can induce in some

patients the complaint of nightmares. This study supports previous studies suggesting that a clear, but currently poorly defined, relationship exists between host defence and infectious disease, and sleep/dreaming.

Other agents reported to induce nightmares

Dream and nightmare recall, dream reports and reports of dream effects on waking behavior are often not included in the parameters of medication types that are not generally considered psychotropic in effect. Many non-psychotropic drugs and older pharmacological agents that could potentially alter dreaming and nightmare induction have not been studied systematically. The CNS side effects of daytime somnolence and/or insomnia may be an indicator for drugs likely to induce disordered dreaming and nightmares (Table 3). Other agents are included in Table 3 for which no causal relationship for patient complaints of nightmares is postulated.

CONCLUSION

A diverse group of pharmacological preparations, both psychotropic and otherwise, are reported to induce nightmares based on clinical trials and case reports. In order to review the current status of knowledge of medication effects on nightmares, we are forced to be specific as to the different phenomenon described as nightmare and the methodology describing the collection of that data. Clinical trial reporting of dreaming side effects may be affected by expectations of both researcher and patients, and in some cases may not be queried based on a lack of known behavioral effects attributable to the studied agent. This study suggests that alteration of dreaming and nightmare occurrence should be considered as possible in clinical trials affecting both agents for which a possible theoretical basis for nightmare induction exists as well as for agents for which no current mechanism has been proposed (Table 3).

This study demonstrates that the clinical use of pharmacological agents affecting the neurotransmitters norepinephrine, serotonin and dopamine are associated with the complaint of nightmares. Agents affecting the neurotransmitters GABA, acetylcholine and histamine are less likely to be associated with the complaint of nightmares. Agents affecting the sleep related immunological response to infectious disease induce nightmares for some patients. By utilizing our current experimental and theoretical knowledge base relating to neurochemical and cognitive variables altering reports of dreaming and nightmares, the potential etiology of a majority of reported drug effects on nightmares can be classified. This approach provides a clinical and theoretical framework useful in categorizing the potential and reported drug effects on nightmares.

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