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REVIEW

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Polysomnographic effects of hypnotic drugs

A review

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Abstract This review aims at providing a critical assessment of the effects of the most widely used benzodiazepine (flurazepam, flunitrazepam, temazepam, triazolam) and non-benzodiazepine (zopiclone and zolpidem) hypnotic drugs, based on the recording of polysomnographic variables. In the light of newly acquired neurophysiological data on the microstructure of sleep, this paper reconsiders the problem of insomnia and the current ideas on polysomnography and hypnotic drugs.

Key words Sleep · Hypnotic drugs · Polysomnography · Insomnia

Introduction

Polysomnography (PSG) is the monitoring of multiple electrophysiological parameters during sleep and it classically includes measurement of electroencephalographic (EEG) activity, eye movements and electromyographic activity. Additional PSG measures can be used to monitor respiration or detect abnormal movements during sleep. PSG techniques can be also used to quantify daytime sleepiness. The most common daytime procedure is the Multiple Sleep Latency Test (MSLT), in which the individual is instructed to lie down in a dark room and not resist falling asleep. The test is repeated five times during the day at 2-h intervals.

In normal subjects, sleep is entered through non-rapid eye movement (NREM) sleep. NREM sleep is composed of four stages characterized by increasing arousal thresholds. During stage 1 (S1), the EEG shows a progressive shift from alpha to theta activity associated with slow, rolling eye movements. Stage 2 (S2) is identified by the appearance of sleep spindles and K-complexes on EEG against a theta/delta background. Stage 3 (S3) begins when high-voltage slow waves comprise greater than 20% and less than 50% of the recording epoch, while stage 4 (S4) is identified by slow waves comprising more than 50% of the recording epoch. The distinction between S3 and S4 is arbitrary, as the physiological characteristics of these stages are almost identical. Indeed, S3 and S4 are often combined and termed as slow wave sleep (SWS).

NREM sleep alternates periodically with rapid eye movement (REM) sleep. About 70–100 min after sleep onset, NREM sleep is replaced by REM sleep characterized by rapid and conjugate eye movements, muscle atonia and theta EEG activity. The development of these sleep patterns along the night allow the quantitative determination of a series of PSG parameters:

total sleep time (TST): actual time spent asleep;
time in bed (TIB): time spent in bed;
sleep efficiency (SE): the ratio of TST to TIB;
sleep latency (SL): the amount of time required to fall asleep;
wake after sleep onset (WASO): the amount of wake time after initial sleep onset and before final awakening;
NREM sleep stages (S1, S2, S3, S4);
REM sleep;
REM latency (REM-L): latency to the first appearance of stage REM sleep;
total wake time (TWT): total amount of wakefulness.

When dealing with PSG, it is necessary to comment on the terms EEG synchronization and desynchronization. EEG synchrony, in the context of sleep, is generally applied to the high voltage slow activity of NREM stages 3 and 4 (SWS). In contrast, the term desynchronized as applied to a mixed frequency pattern consisting mainly of low amplitude theta (4–7 Hz) and fast activity (14 Hz and above). The terms are also applied to the shift from the high voltage slow activity of NREM sleep (EEG synchronization) to the low-voltage mixed frequency pattern of REM sleep (EEG desynchronization).

The PSG parameters have a characteristic temporal organization during the night. REM sleep alternates with NREM sleep at about 90 to 120-min intervals. SWS tends to occur in the first half of the night, while stage 2

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and REM sleep increase in duration in the second half. Despite a certain degree of variability, the amount of nocturnal sleep stages is relatively constant. About 20–25% of total sleep is occupied by REM sleep, while the remaining 75–80% consists of NREM sleep (stage 1: 5%; stage 2: 50%; stages 3 and 4: 20–25%). The volume and distribution of the standard PSG parameters reflect the macrostructure of sleep.

The macrostructural pattern of sleep can be affected by a variety of endogeneous (aging) or exogenous (noise) factors. In the elderly, PSG changes consist of increased WASO and S1, and decreased SWS. PSG parameters may be strongly affected also by drugs including the compounds prescribed in the treatment of sleep disorders.

Treatment of insomnia: from barbiturates to non-benzodiazepines

Hypnotic drugs have long been used to treat insomnia. Until 1960, the therapeutical approach to sleep disorders was dominated by barbiturates. These are drugs with a depressive action on both cortical and subcortical areas. As a result, important centres in the brainstem regulating vegetative functions are inhibited, and intoxication may thus be fatal. Barbiturates also carry a rather high risk of addiction.

From the beginning of the 1960s, benzodiazepines (BDZs) have replaced barbiturates in the treatment of insomnia. Compared to barbiturates, BDZs have little or no effect on centres in the brainstem and therefore intoxication carries very little risk of fatal outcome. Another advantage of the BDZs is that the risk of abuse is definitely smaller than that of barbiturates. Thus, due to their easy management and proven efficacy, the BDZs have occupied a leading place among the hypnotic drugs most commonly used in clinical practice. Still, an excessive depression of the CNS can be a common side effect of BDZs in routine clinical use.

Newer compounds acting at the BDZ site, although not sharing the classical BDZ chemical structure, have recently been introduced to avoid some of these inconveniences. In particular, the introduction of sedative non-BDZ compounds (zolpidem and zopiclone) offering the therapeutic effects of classical BDZs, but with less adverse effects, has further potentiated the clinical role of GABA-ergic drugs. In fact, the major central actions of these agents – their anxiolytic, anticonvulsant, muscle-relaxant, and sedative-anesthetic properties – are mediated by GABA receptors. Both BDZs and non-BDZs bind to $GABA_A$ receptors to increase the affinity of the receptors for GABA as well as the frequency of GABA-activated channel openings (Macdonald and Twyman 1991).

Insomnia and anxiety: common and different traits

The fact that BDZs are endowed with both anxiolytic and sedative effects has prompted the equation insomnia=symptom of anxiety. Insomnia and anxiety probably share some common cerebral mechanisms (Gaillard 1994), and several forms of insomnia are certainly supported by underlying mental problems. According to the DSM-IV (1994), approximately 15–25% of individuals with chronic insomnia are diagnosed with primary insomnia (a sleep disturbance not caused by a mental disorder), while a concomitant psychiatric diagnosis is seen in 25–50% of patients complaining of insomnia (Coleman 1983; Tan et al. 1984; Jacobs et al. 1988). In addition, it is a common clinical experience that not all subjects with anxiety disorders complain about sleep. Several authors have noted that the prevalence of anxiety disorder diagnoses within samples of insomniacs is low. In particular, Tan et al. (1984) found that only 15% of patients presenting at a sleep disorders center qualified for an anxiety disorder diagnosis. From a more general viewpoint, the idea that insomnia simply reflects anxiety, depression or a weakness of character needs to be revised (Lader et al. 1992). Indeed, several cases of insomnia may have a non-psychiatric aetiology and only secondarily develop a mental discomfort or may be initially triggered by a psychological problem and then continue as a self-sustained complaint, even when the causing factor has been eliminated. Moreover, "the clinical picture of all patients with insomnia associated with an anxiety disorder may be clouded by the use of, or withdrawal from, psychotropic agents. In many instances, the nature and degree of sleep disruptions may be related more closely to the drug use than to the psychiatric disorder" (Walsh et al. 1994).

These considerations have also therapeutical repercussions. The recommended use of hypnotics should not exceed the 4–6 weeks duration, whereas the maintainance therapy with BDZs in generalized anxiety disorder should have a minimum duration of 4–6 months (Rickels et al. 1994). Thus, an adequate assessment of insomnia (primary or secondary to anxiety) is crucial for establishing the treatment strategies.

Is the macrostructure of sleep adequate to investigate insomnia?

Insomnia is a complaint of inadequate or abnormal sleep. Insomniacs describe difficulties falling asleep, frequent nocturnal arousals, early morning awakenings, a short sleep time, and nonrestorative sleep. Thus, the expected PSG findings in these patients should be longer SL, shorter TST and SE, augmented WASO and S1, reduced SWS, and anticipation of final awakening. However, there is a great body of evidence that in many cases insomniac patients cannot be distinguished from normal sleepers on the basis of the traditional scoring criteria (Carskadon et al. 1976). Buysse and Reynolds (1990) actually state that "the magnitude of PSG differences between insomniacs and controls is small, and not all studies report abnormalities in each measure. In addition, sleep-stage architecture does not appear to be abnormal

in chronic insomnia." Other authors admit that "the subjective complaint of insomnia is not confirmed with PSG measures" and that "psychoactive drugs might affect sleep patterns even when the subjective complaint is not objectively substantiated" (Declerck et al. 1992). In short, these observations indicate that the macrostructure of sleep provides scarce information to: a) discriminate insomniac patients from controls; b) differentiate between transient, short-term and long-term insomnia; c) monitor the effects of hypnotic drugs.

New PSG perspectives: proposals to overcome macrostructural limitations

If on the one side the assessment of the macrostructure, seen as a succession of stable states and abrupt transitions, has provided common bases for agreement on certain PSG features, on the other side it has coated the dynamic process of sleep into a rigid, stepwise framework. Additionally, as no clear neurophysiological definition has been attributed to the conventional sleep stages identified, poor relevance can be ascribed to the effects that a hypnotic drug can provoke on the macrostructural parameters. The great majority of PSG studies on hypnotic compounds report some alteration of PSG variables. However, the neurophysiological meaning of these changes often remains to be clarified.

The relatively small benefits of a hypnotic drug on PSG measures can be also related to the abnormal perception of physiological events, including sleep and wakefulness, reported by patients with insomnia. Insomniac can overestimate the degree of their disturbance, while BDZs may alter insomniacs' perception of sleep. With respect to the so-called sleep state misperception, the International Classification of Sleep Disorders (Thorpy 1990) suggests that "excessive mentation during sleep may contribute to the sensation of being awake", and also that "physiological abnormalities may exit in the sleep tracing that are too subtle to be detected by recording methods currently in use". In short, subjective evaluation may deeply differ from objective changes in PSG as it is currently measured.

A) Attempts to overcome the bias between subjective and objective evaluation have been made using quantitative measures of EEG activity. EEG parameters during sleep can be assessed by computer-aided methods of signal analysis (e.g., spectral analysis, period amplitude analysis). This not only allows the quantitative determination of the underlying EEG components (delta, theta, alpha, sigma, beta), but also makes it possible to delineate the time course of these frequencies during sleep. The exponential decay of delta activity along the night – referred to as the homeostatic process of sleep regulation – actually parallels the macrostructural distribution of SWS (Borbely 1982). The homeostatic process is regarded as an indicator of sleep intensity, which is high during the initial part of the sleep episode and gradually declines with the progression of sleep. There is strong evidence that the level of slow wave activity (SWA) is determined by the duration of prior waking. Thus, an increase of the homeostatic intensity should be observed whenever sleep (especially SWS) is prevented or disturbed. To date, the homeostatic aspects in sleep regulation have been heavily applied to sleep deprivation, but not to insomnia. Some alternative procedures have attempted to exploit clinically the information supplied by delta activity (Gaillard 1979; Rosadini et al. 1992). These methods offer a dynamic outline of sleep regulation, but still overlook the many forms of microadjustments occurring incessantly during the course sleep.

B) According to the standard scoring system (Rechtschaffen and Kales 1968), the sleep recording is divided in epochs of 20 or 30 s. Each epoch is assigned a score that most appropriately characterizes the predominant pattern occurring during that interval. Thus, short-lived events occurring within an epoch but not descriptive of the majority of the epoch may be overlooked. Both spectral analysis and traditional PSG parameters actually obliterate a series of micro-events and subliminal adjustments that underlie the apparent stability of sleep stages. These microadjustments, known as phasic events, constitute the short-lasting adaptive responses of the brain to all internal and external sources of perturbation while preserving the continuity of sleep (Halasz and Ujszaszi 1991). Morphologically, these brief adjustments are characterized by bursts of EEG slowing (sequences of k-complexes, delta bursts) or speeding (alpha or beta activity), often concomitant with increases in muscle tone and neurovegetative activities. Functionally, most of these phasic events correspond to transient arousals.

It is known that arousals undergo physiological age-related modifications (Mathur and Douglas 1995), but their count has failed to be related to a complaint of "nonrestorative" sleep. Rather, consistent neurophysiological information can be derived from their sequential arrangement. In effect, EEG arousals are not randomly distributed throughout sleep, but tend to recur at 20 to 40-s intervals, suggesting that there is a natural arousal rhythm in the EEG of sleep (Terzano and Parrino 1991; Terzano et al. 1985, 1996). This rhythm is known as the Cyclic Alternating Pattern (CAP). The CAP scoring criteria allow the quantative determination of EEG phasic events within a periodic framework. CAP methodology has been extensively applied in normal conditions and in several sleep disorders (Terzano et al. 1985, 1988a; Terzano and Parrino 1992, 1993), and there is neurophysiological evidence that, regardless of the specific condition, CAP translates a sustained instability of the arousal level (Terzano et al. 1985, 1988a). The percentage ratio of CAP time to NREM sleep time supplies the microstructural parameter of CAP rate. In normal sleep, CAP rate ranges between 25 and 45%, while it is increased by disturbing factors of different nature (noise, periodic leg movements, nocturnal apneas, epileptic phenomena). CAP rate is characterized by a low intra- and inter-individual variability within a given decade of age and correlates well with the subjective appreciation of sleep quali-

ty (Terzano et al. 1990a; Terzano and Parrino 1992). In untreated subjects, amounts of CAP rate exceeding 60% invariably result in serious disruption of sleep structure. Accordingly, pathological values of CAP rate can be reduced by administration of drugs with hypnotic properties (Terzano and Parrino 1993).

Why a review on PSG effects of hypnotic drugs?

Surveys in industrialized Western countries indicate insomnia as a significant public health problem affecting a substantial percentage of the population. The 1991 Gallup survey reported that 36% of respondents complained of insomnia, with 9% reporting that it was a chronic problem (The Gallup Organization 1991). These data have been confirmed by a meta-analytic review of several epidemiological surveys (Lack and Thorn 1991). The prevalence of insomnia has repercussions also on the administration of hypnotic drugs. A recent national investigation conducted in Italy reports that over 4 million adults use hypnotic drugs, and that the latter are taken on a regular basis by over 1200000 individuals (Granella et al. 1995).

Although insomnia is the most common of all sleep complaints, the use of PSG is not recommended for the evaluation of either transient or chronic insomnia (Reite et al. 1995). First of all, PSG investigation is not cost-effective due to time and technical limitations. In addition, several cases of insomnia may have no specific PSG abnormality. In other words, it seems more useful to establish the subjective appreciation of sleep quality rather than to determine the alterations of sleep structure.

The present review aims at exploring under a critical viewpoint the PSG effects of hypnotic drugs on human sleep. In particular, it focuses on commonly prescribed BDZ hypnotics (flurazepam, flunitrazepam, temazepam, triazolam) and on novel non-BDZ hypnotics (zopiclone, zolpidem) on which a certain amount of reliable trials have been carried out.

The contributions referred to the single drugs were subdivided in those regarding healthy subjects (either under standard recording conditions or situational insomnia) and insomniac patients, respectively.

When specified, insomniac patients and poor sleepers complained of a latency of 30–45 min to fall asleep nightly, and/or less than 6–6.5 h total sleep duration, and/or at least three nocturnal awakenings. Insomnia was defined as chronic when the disturbance of sleep initiation and maintenance persisted for at least 1 month.

For both BDZs and non-BDZs, the sequence of presentation was empirically based on the kinetic properties of the single compound. Whereas some articles described multi-drug comparisons, in this review the PSG properties of the single compounds were evaluated separately. All comparisons were related to significant differences of drug treatment versus placebo. A ranking of the drugs reviewed as to their PSG effects is supplied following the presentation of the individual compounds.

Our aim at selecting rigorously accomplished contributions has not prevented the inclusion of pioneering papers lacking the latest valuable methodological issues (e.g., double-blind framework). A careful review of the literature was carried out for this paper, although we are aware that some important study might have been involuntarily omitted.

BDZ hypnotics

Flurazepam (half-life: >40 h)

Healthy volunteers

Standard conditions. In single dose administration, flurazepam 30 mg decreases TWT and increases TST, S2 and REM sleep, while flurazepam 15 mg is statistically similar to placebo. Both doses (15 mg and 30 mg) are followed by residual effects in morning, afternoon and evening periods of the day after administration (Ogura et al. 1980). Both in young and middle-aged subjects, a single bedtime dose of flurazepam 30 mg depresses slow wave activity or SWA (0.5–4.5 Hz) over the entire sleep period (Wright et al. 1986) and enhances the occurrence of abortive first REM sleep episodes (low level of SWA without rapid eye movements and/or muscle relaxation). However, the declining trend of SWA over the first three cycles and the alternating pattern of NREM and REM sleep are not disrupted (Borbely et al. 1983; Borbely and Achermann 1991). Flurazepam 30 mg in single dose also increases the frequency of sleep spindles. The changes of spindles and SWA are similar in the drug night and in the post-drug night (Azumi and Shirakawa 1982; Borbely et al. 1983; Borbely and Achermann 1991).

Flurazepam 15, 26 and 45 mg for 2 nights increases TST and shortens the time to fall asleep and the number of WASO. During the first night, the drug induces a dose-related reduction of SWS, REM sleep, REM density, delta and alpha activities and a dose-related increase of S2, sigma and beta activity. On the second night of drug administration, SWS and delta activity decrease at all dose levels (Karacan et al. 1981).

A decrease of SWS is also observed when flurazepam 30 mg is taken on a longer (7–14 days) time basis (Weitzman and Pollak 1982; Roehrs et al. 1986a), and the suppression of S4 persists unchanged during a 3-day withdrawal period (Feinberg et al. 1979). Administration of flurazepam 30 mg within a 2-week range decreases TWT, REM sleep, and rapid eye movements, and increases TST, S2, and REM-L. Owing to the long elimination half-life, the mean sleep latency on the MSLT is reduced by the drug along the entire period of treatment (Roehrs et al. 1986a), but there are no signs of rebound insomnia (Feinberg et al. 1979).

Insomniac patients

In the 7- to 14-day period, flurazepam 30 mg increases TST, SE, S2, REM-L, and reduces WASO, SL, S1, REM sleep, and SWS (Bliwise et al. 1983; Quadens et al. 1983; Kripke et al. 1990). The doses of 15 mg and 30 mg produce the same improvement in SL, WASO, and SE. A gradual decrease in delta amplitude and count, and a gradual increase in sleep spindle rate are also observed (Johnson et al. 1979). Effectiveness of the hypnotic action is present throughout drug administration (Roehrs et al. 1982), as well as daytime sleepiness assessed by MSLT (Bliwise et al. 1983).

In chronic insomniacs, a slight loss of effectiveness emerges with a longer administration (3–4 weeks) of flurazepam 30 mg. In particular, while the drug-induced reduction in REM sleep, REM density, and TWT is more prominent with short- or intermediate-term use (McClure et al. 1988), SWS remains markedly suppressed throughout the entire intake period. SWS recovers slightly after initial discontinuation (Kales et al. 1976). No rebound is noted after withdrawal (Kales et al. 1975).

Flurazepam 30 mg received by middle-aged insomniacs for more than 4 weeks (37 nights) induces increase in the spindle rate and reduction of delta count per minute, particularly in the last part of the treatment. Full return to baseline values is observed only after 10 days of withdrawal (Johnson et al. 1983).

Limited information is available on aged insomniacs. TST and S2 are increased and arousals decreased when flurazepam 30 mg is administered for 3 consecutive nights in elderly subjects with chronic insomnia. The MSLT score shows increased sleepiness (Carskadon et al. 1982).

Flurazepam synopsis

In healthy volunteers, flurazepam increases sleep duration, stage 2 sleep, and the spindle rate, and decreases slow wave sleep (especially stage 4) with reduction of the delta power.

In insomniacs, flurazepam increases total sleep time, sleep efficiency and decreases stage REM and slow wave sleep.

There is no evidence of rebound insomnia, but sleep latency is shorter under MSLT. These effects are found both under short- and long-term administration of the drug.

In elderly insomniacs, flurazepam makes sleep longer and more stable, but there is evidence of daytime sleepiness, objectively detected under MSLT.

Flunitrazepam (half-life: 25 h)

Healthy volunteers

Standard conditions. In young adults, a single dose night with flunitrazepam 2 mg increases TST, SE, REM-L, S2, S4 (only in the first 2 h), and enhances the occurrence of abortive first REM sleep episodes. The drug also reduces SL, time and number of WASO, REM sleep, REM density, amount of stage shifts, number of body movements, and S4 (in the later part of sleep hours). Alpha activity is increased in SWS and spindles are much more abundant throughout NREM sleep. NREM sleep theta and delta activities, and k-complexes are markedly reduced by the drug, but the declining trend of SWA over the first three cycles and the ultradian pattern of sleep regulation are not disrupted. In the post-drug placebo night, modifications persist for theta and delta activities, and for k-complexes, whereas alpha activity recovers the baseline value. There is disagreement on the modifications of spindles during the withdrawal phase. According to Gaillard and Blois (1989), the post-drug night is characterized by a complete recovery of baseline spindles, while Borbely et al. (1983; Borbely and Acherman 1991) report that the changes of sleep spindles persist in the subsequent drug-free night. A carryover increase of spindles is described during the first 2 nights of the withdrawal phase following a 5-night intake of flunitrazepam 2 mg (Azumi and Shirakawa 1982).

Situational insomnia. On daytime sleep, flunitrazepam 0.25 mg and 0.50 mg produces a reduction in WASO and an increase in SE. With 0.50 mg there is also an increase in TST, S2 and REM-L (Nicholson et al. 1980).

In young adults, both under a 6-h advanced shift (A-shift) and a 6-h delayed shift (D-shift) of the sleep-wake schedule, flunitrazepam 1 mg increases TST, SE and S2. Sleep latency, WASO, S1, and SWS are shortened only during the A-shift, while REM sleep is reduced exclusively in the S-shift (Kanno et al. 1993).

Insomniac patients

Although from the beginning flunitrazepam has been indicated as a hypnotic drug, the PSG effects of this compound on insomniac patients have been investigated in a limited number of studies. In our opinion, the most convincing information on the long-term use of this drug was provided as early as the pioneering study of Scharf et al. (1979). In that paper, the authors describe a 4-week administration of flunitrazepam 2 mg nightly to middle-aged subjects with a history of insomnia. PSG investigation is accomplished on nights 2–4 (baseline measurements), on nights 5–7 (initial and short-term drug effectiveness), on nights 16–18 (intermediate-term), and on nights 30–32 (long-term). Short-term and long-term withdrawal effects are also monitored on nights 33–35 and 45–47, respectively. Flunitrazepam causes increase of SE, reduction of TWT, number and duration of WASO only in the initial and short-term phase. REM sleep is decreased only on nights 5–7, while there is a decrease of S3 with short-term administration and a further reduction in the intermediate and long-term period. Partial recovery of S3 baseline values is found only in the late with-

drawal phase. S4 is only minimally present on baseline nights and is completely absent throughout drug administration. Following withdrawal, S4 returns to the low baseline values. Rebound insomnia (increased SL, TWT, number of WASO and decreased SE) occurs as a short-term withdrawal sign.

More recently, flunitrazepam 2 mg was administered for 3 nights in non-pregnant women complaining about chronic insominia. The drug shortens SL and REM sleep, and prolongs S2 and REM-L. The drug also increases SWS and reduces WASO in the first 2 h of sleep. Spectral analysis reveals enhancement of delta activity during the first 2-h period of sleep time and a reduction of delta activity during the second and third 2-h period of sleep (Declerck et al. 1992).

Flunitrazepam synopsis

In healthy volunteers, flunitrazepam increases total sleep time, sleep efficiency, stage 2 sleep and REM latency, and shortens sleep latency, stage REM, stage 4, and slow wave sleep. These macrostructural findings are paralleled by a decrease in delta and slow wave activity and by an increase of spindles. These effects occur both under single dose and after prolonged intake.

In insomniacs, short-term flunitrazepam increases SWS only in the first 2 h of sleep. Flunitrazepam causes reduction of slow wave sleep. Rebound insomnia is described after long-lasting treatment.

Temazepam (half-life: 9.5–12.4 h)

Healthy volunteers

Standard conditions. Temazepam 20 mg in single dose reduces SL, WASO and S1, while increasing REM sleep. In the same study, temazepam 20 mg plus ethanol determines a reduction of REM sleep and the time to fall asleep becomes even shorter (Lehmann and Liljenberg 1981).

Temazepam 30 mg in single dose reduces the number of stage changes, the number of WASO, the amount of S1 and S4, while increasing SE and S2. Spectral analysis shows an increase in the more rapid EEG frequencies and disruption of the periodicity of delta activities (Ferrillo et al. 1984).

Temazepam 30 mg taken for 9 nights increases TST, reduces the number of awakenings and shortens S1 and the latency to persistent sleep during the early phase (nights 1–2). REM sleep is reduced only in the late phase (night 8–9), while the increase of S2 is a persistent finding. Mean sleep latency on the MSLT is reduced by temazepam 30 mg only during the early phase of treatment (Roehrs et al. 1986a).

Situational insomnia. When administered to adults not suffering from sleep disorders but in transitory "first night effect" insomnia', temazepam 7.5 mg in single dose increases TST, SE and S2, and reduces S1. Under the same recording condition, temazepam 15 mg and 30 mg causes linear variations in sleep parameters, while TWT is reduced only by the higher dose of the drug (Roehrs et al. 1990).

Insomniac patients

In sleep onset insomnia, acute (days 1–3) and short term (days 7–9) administration of temazepam (15 mg and 30 mg) is effective in reducing SL and prolonging TST. Alterations in sleep staging pattern (increase of S2, reduction of SWS and REM sleep) appear to be dose-dependent with more marked effects under 30 mg. No evidence of sleep disorders is found after withdrawal of the drug taken for 3 nights (Roehrs et al. 1984, 1986b).

In young and middle-aged subjects with chronic insomnia, temazepam increases TST. There is no indication of tolerance for as long as 5 weeks at the 30 mg dose (Miltler et al. 1979), but this dose may induce rebound for TST after discontinuation (Scharf et al. 1990). Acute administration of temazepam causes a decrease (15 mg and 30 mg) or no improvement (20 mg) in SWS (Beary et al. 1984; Scharf et al. 1990). Temazepam 20 mg in single dose enhances SE and S2 and reduces upward stage shifts (from SWS to S1 and S2) and the time to fall asleep (Beary et al. 1984). The decrease of SL is also observed when temazepam (15 mg and 30 mg) is administered over a 14-day period (Scharf et al. 1990).

In elderly insomniacs, temazepam 7.5 mg used for 7 nights reduces TWT. No signs of rebound insomnia are reported following drug withdrawal (Vgontzas et al. 1994).

In patients with periodic nocturnal myoclonus, the administration of temazepam 30 mg for 7 days prolongs TST, SE and S2, while shortening SL and SWS and reducing the number of WASO. No significant reduction occurs in the number of nocturnal jerks, but there is a significant fall in the number of twitches per hour of sleep (Mitler et al. 1986).

Temazepam synopsis

In healthy volunteers, temazepam is especially effective in increasing stage 2 and reducing the time to fall asleep, intrasleep wakefulness, stage 1, and stage 4. The latter finding is corroborated by a disruption of delta activities.

In insomniac patients, temazepam potentiates sleep duration and stage 2, and curtails sleep latency and slow wave sleep. The latter is more pronounced under the higher doses of the drug (30 mg). The slow wave sleep suppression persists even after prolonged intake. No signs of rebound insomnia are reported in elderly insomniacs.

A significant fall in the number of twitches per hour of sleep is reported in periodic nocturnal myoclonus.

Shorter sleep latencies on MSLT correlate with no evidence of rebound insomnia after abrupt discontinuation of the compound.

Triazolam (half-life: 1.5–5.5 h)

Healthy volunteers

Standard conditions. In adults, triazolam 0.50 mg reduces SL, WASO, S1 and REM sleep and increases TST, S2, and REM-L (Ogura et al. 1980; Lund et al. 1988). Mamelak et al. (1990) report instead a decrease of REM-L. Triazolam 0.50 mg taken at bedtime for 3 consecutive days reduces SL, the number and the duration of WASO and SWS (Copinschi et al. 1990).

Similarly to what happens with flurazepam and flunitrazepam, which, however, have a long elimination half-life, a single bedtime dose of triazolam 0.50 mg enhances the occurrence of abortive first REM sleep episodes, increases the activity in the frequency of sleep spindles, and depresses SWA over the entire sleep period. The drug-night depression of SWA persists in the post-drug night. However, the declining trend of SWA over the first three cycles and the ultradian pattern of sleep regulation are not disrupted (Borbely et al. 1983; Borbely and Achermann 1991).

In single administration, triazolam 0.25 mg and 0.50 mg increase TST, S2 and reduce SL and WASO. Both doses produce slight residual effects on the morning period after administration (Ogura et al. 1980). The suspension of triazolam 0.50 mg decreases SWS duration on the first night of withdrawal (Mamelak et al. 1990).

On a 6-consecutive-night protocol, triazolam 0.25 mg and 0.50 mg increase TST on the last drug night. The 0.50 mg dose is no more effective than 0.25 mg, but induces rebound insomnia (Roehrs et al. 1986c).

In young volunteers, triazolam 0.25 mg, when taken along a short-term period, alters the regularity of delta profile. In particular, the drug induces a longer first and second cycle, an increase of delta activity in the first two cycles and a faster decline in SWA in the last cycle (Ferrillo et al. 1992).

Situational insomnia. It has been observed that no overall differences between placebo and triazolam 0.25 mg are found in young subjects who sleep in economy class airline seats (Aeschbach et al. 1992).

In subjects allowed to sleep for 6 h during the day in unfavourable conditions (sitting upright in a well-lit crowded chamber), following 24 h of sleep deprivation, a single dose of triazolam produces an increase in SWS (0.125 mg, 0.25 mg and 0.50 mg) and a reduction in WASO (0.50 mg) (Balkin et al. 1989).

Intermittent white noise (WN) or methylphenidate (MPD) reduce SE (only with MPD), TST, and REM sleep, and increase WASO. The simultaneous administration of triazolam 0.25 mg produces an almost complete recovery from the sleep disturbances induced by WN or MPD except for the reduction of REM sleep (Okuma and Honda 1978).

In young adults, both under a 6-h advanced shift (A-shift) and a 6-h delayed shift (D-shift) of the sleep-wake schedule, triazolam 0.25 mg increases TST, SE and reduces nocturnal awakenings. SWS is increased in the D-shift and decreased in the A-shift (Kanno et al. 1993).

In rotating shift-workers studied in the morning after a night shift, triazolam 0.50 mg induces an increase in TST, SE and S2, with a reduction in S1 and WASO. No adaptation to daytime sleep is seen during the sleep periods without the drug (Walsh et al. 1984).

On daytime sleep, triazolam 0.25 mg and 0.50 mg produce a reduction in WASO and an increase in SE. In addition, with 0.50 mg there is also an increase in TST, S2 and REM-L (Nicholson et al. 1980).

In healthy subjects, triazolam 0.25 mg, when given during both basal and perturbed conditions, reduces the noise-induced enhancement of CAP rate (Terzano et al. 1995, Parrino et al. 1996).

Insomniac patients

In sleep-onset insomnia recorded on a 5-consecutive-night protocol, administration of triazolam 0.25 mg and 0.50 mg induces similar reductions in SL and SWS and similar increases in S2 and SE (Johnson et al. 1987).

In young poor sleepers, triazolam 0.50 mg for 6 consecutive nights induces an increase in spindles and a reduction in the delta count during the period of drug administration. Both values return to baseline on the first withdrawal night (Johnson and Spinweber 1981).

In adult patients with chronic insomnia, triazolam 0.50 mg administered for 7 consecutive days increases TST, SE, and S2 and reduces SL, TWT, WASO, S1 and REM sleep. Sleep latency on the MSLT is not decreased by the drug (Bliwise et al. 1983). In insomniac patients, triazolam 0.50 mg is more effective than 0.25 mg. Values for TST, SE, TWT, WASO, REM sleep and SL return to baseline during the 3 post-drug nights with both doses (Vogel et al. 1975).

In chronic insomnia, triazolam 0.5 mg administered on a longer time period (4–5 weeks) lengthens TST, S2 and REM-L in the short-term treatment phase (first 2 nights of drug administration), but there is partial tolerance during intermediate- (after about 10 days of treatment), and long-term use. Increase in the spindle rate and reduction of delta count per minute occurs especially in the latter part of the treatment. In spite of the short elimination half-life of the drug, a full return to the baseline values is observed only 10 days after withdrawal (Johnson et al. 1983) which actually causes rebound insomnia (Monti et al. 1992, 1994).

Both triazolam 0.125 mg and triazolam 0.25 mg, administered on a 2-week basis in patients with chronic insomnia, increase TST, but this effectiveness diminishes with intermediate-term administration. The drug also

causes a decrease in delta sleep in the intermediate period. During withdrawal, rebound for SL and TST and SE is seen with both doses (Scharf et al. 1990).

On a 28-day protocol in chronic insomnia, triazolam 0.25 mg improves SE and TST after acute administration, but this effect vanishes after 4 weeks of treatment. These parameters show signs of rebound in the first withdrawal night, while S2 decreases in the second post-drug recording (Saletu et al. 1994).

Carskadon et al. (1982) report that in elderly subjects suffering from chronic insomnia, triazolam 0.25 mg administered for 3 consecutive nights induces an increase in TST and S2, and a reduction in TWT, latency to S2, and in the number of arousals. The MSLT score shows decreased sleepiness. According to Mouret et al. (1990), however, the same dose administered for 15 days determines an improvement only in SL, which is shortened in the last 3 nights of treatment in comparison with baseline. No signs of rebound insomnia emerge during the nights following drug discontinuation.

Triazolam synopsis

In healthy volunteers, triazolam increases total sleep time, and stage 2 sleep, and reduces sleep latency, intrasleep awakenings, and slow wave sleep. The effects are dose-related. There is evidence of rebound insomnia.

Triazolam is effective in shift-workers and in several conditions of situational insomnia: increase of total sleep time and sleep efficiency, and reduction of nocturnal awakenings and CAP rate.

In clinical insomnia, triazolam increases sleep duration, sleep efficiency, stage 2 sleep and spindle rate, and reduces nocturnal wakefulness and delta activity.

There is no evidence of daytime sleepiness (MSLT), but rebound insomnia is reported. In elderly insomniacs, triazolam shortens the time to fall asleep.

Non-BDZ hypnotics

Zopiclone (half-life: 3.5–6 h)

Healthy volunteers

Standard conditions. During the first 4 h of sleep, no changes of SWS are observed under single dose of zopiclone 5 mg, 7.5 mg and 10 mg. Similarly to what happens with the BDZ flurazepam, spectral analysis reveals a reduction in amplitude of delta wave activity and an increase in the total number of delta waves. These effects occur for the three doses (Wright et al. 1986). Zopiclone 7.5 mg also reduces SWA and enhances spindle frequency activity (Aeschbach et al. 1994). When zopiclone 3.75 mg and 7.5 mg are given for 2 consecutive nights, there is a reduction of WASO, S1, and REM sleep and increased S2. Enhancement of SWS is produced only with the lower dose (Billiard et al. 1989). Zopiclone 10 mg, when taken for 3 consecutive nights, increases S2 and SE and reduces SL and S1 (Okuma et al. 1991; Tsuchiyama et al. 1991).

Situational insomnia. In young adults, both under a 6-h advanced shift (A-shift) and a 6-h delayed shift (D-shift) of the sleep-wake schedule, zoplicone 10 mg increases TST, SE and reduces nocturnal awakenings. During the A-shift, the drug also increases S2 and shortens SL, while SWS in increased only during the D-shift. REM sleep is enhanced in the A-shift and reduced in the D-shift (Kanno et al. 1993).

Zopiclone 7.5 mg, when given during both basal and perturbed conditions, reduces the noise-induced enhancement of CAP rate (Parrino et al. 1996).

Table 1 Effects of hypnotic drugs on sleep structure. *SL* sleep latency, *TST* total sleep time, *SE* sleep efficiency, *WASO* wake after sleep onset, *TWT* total wake time, *S1* stage 1, *S2* stage 2, *S3* stage 3, *S4* stage 4, *SWS* slow wave sleep, *SREM* REM sleep, *REM-L* latency to REM sleep, *PLM* periodic leg movement disorder, *R* rebound, *C* carryover, *H* healthy volunteers, insomniac patients, ↑ increase, ↓ decrease, = no change, ↓↑ decrease or increase

		SL	TST	SE	WASO	TWT	S1	S2	S3	S4	SWS	SREM	REM-L
Temazepam	H	↓	↑	↑	↓		↓	↑	=	↓		↓↑	
7, 15, 20, 30 mg	I	↓	↑	↑	↓ (PLM)	↓ 30 mg	↓	↑	=	=	↓	↓ 30 mg	
Flunitrazepam	H	↓	↑	↑	↓			↑		↓		↓	↑
0.25, 0.5, 2.0 mg	I	↓	↑		↓			↑			↓	↓	
Flurazepam	H	↓	↑		↓	↓		↑		↓	↓	↓	↑
15, 20, 30, 45 mg	I	↓	↑ (R)	↑	↓ (R)		↓	↑		↓	↓	↓ (C)	↑ (R)
Triazolam	H	↓	↑ (R)		↓ (R)		↓	↑			↓ (C)	↓	↓↑
0.125, 0.25, 0.5 mg	I	↓ (R)	↑ (R)	↑ (R)	↓ (R)	↓	↓	↑			↓	↓ (C)	↑
Zopiclone	H	↓	↑	↑	↓	↓	↓	↑			↓	↓	↑
3.75–5, 7.5–10 mg	I	↓	↑	↑	↓	↓	↓	↑			=	↓	↑
Zolpidem	H	↓	=	↑	↓	↓	↓	=	=	=	↓	↓ ≥20 mg	=
5–10, 15–20, 30–40 mg	I	↓	↑ (C)	↑	↓	↓		↑ (C)		↑	↑ (C)	↓↑	↓ 20 mg

Table 2 Effects of hypnotic drugs on EEG components. *Sigma* EEG activity between 12 Hz and 14 Hz, *Delta* EEG activity below 4 Hz, *Theta* EEG activity between 4 Hz and 7.5 Hz, *Alfa* EEG activity between 8 Hz and 12 Hz, *Fast* EEG activity above 15 Hz, *C* carryover, *H* healthy volunteers, *I* insomniac patients, ↑ increase, ↓ decrease, = no change

		Sigma	Delta	Theta	Alfa	Fast
Temazepam	H		↓	↓		↑
7, 15, 20, 30 mg	I					
Flunitrazepam	H	↑ (C)	↓ (C)		↑	
2 mg	I	↑	↓			↑
Flurazepam	H	↑ (C)	↓ (C)		↓	↑
15–26–30 mg	I	↑ (C)	↓ (C)			
Triazolam	H	↑	↓ (C)			
0.25–0.50 mg	I	↑ (C)	↑ (C)			
Zopiclone	H	↑	↓			
5–7.5–10 mg	I					
Zolpidem	H	= 40 mg	↓ 40 mg	↓ 40 mg		
10–40 mg	I	↑		↓		

Insomniac patients

In adults with chronic insomnia, zopiclone 7.5 mg administered for at least 2 weeks shortens SL and S2, reduces the number of awakenings and the period of WASO, and increases TST, SWS, and REM-L. Efficacy is immediate, persists with drug administration, and even 1 week after drug withdrawal (Jovanovic and Dreyfus 1983). Similar findings are reported in a group of menopausal women with chronic insomnia, taking zopiclone 7.5 mg for 13 days. In these patients, however, the drug induces a decrease of SWS that undergoes a slight improvement only during the withdrawal period (Quadens et al. 1983). A decrease of SWS is described also when zopiclone 7.5 mg is administered in adult patients with chronic insomnia over a 3-week treatment period (Mamelak et al. 1983). In all the three studies, however, no sign of rebound insomnia is found when the drug is discontinued.

In elderly patients suffering from chronic insomnia, zopiclone 7.5 mg, when administered for 15 days, increases TST, SE, S2, REM sleep, and SWS in the initial treatment period (days 1–3). The initial enhancement of SWS persists in the final treatment period (days 13–15) also characterized by an increase in TST and S2. No signs of rebound insomnia emerge in the 3 nights following drug discontinuation, during which the increase in SWS persists (Mouret et al. 1990).

A revision on the effects of zopiclone on 78 healthy volunteers and 95 patients with insomnia shows (Mouret 1992):

– a systematic increase in TST in middle-aged insomniacs, but little or no modification of these parameters in healthy younger subjects;
– a reduction in S1 and an increase in S2 in both groups;
– an increase (or more often no change) in SWS, particularly in insomniac subjects;
– a reduction in REM sleep, particularly in healthy subjects;
– absence of rebound phenomena on withdrawal of the drug;
– that most of these studies were conducted for 2–3 weeks: the revision also includes two trials based on treatment periods of 54 (Pecknold et al. 1990) and 183 nights (Fleming et al. 1988), respectively.
– that the dose most frequently administered was 7.5 mg. With the exception of SWS, which remained unaltered until the last dose of 10 mg, all the changes in the sleep stages and in TST were dose-dependent.

These results are largely confirmed in another review compiled by Musch and Maillard (1990).

Spectral analysis reveals that zopiclone is also a spindle enhancing drug (Iwata et al. 1989; Trachsel et al. 1990).

Zopiclone synopsis

In healthy volunteers, zopiclone prolongs sleep duration and stage 2 sleep, and reduces nocturnal awakenings, sleep latency, and stages 1 and REM.

In conditions of insomnia, zopiclone increases total sleep time and REM latency, and curtails nocturnal awakenings, sleep latency, and CAP rate. The changes in the sleep stages are dose-dependent.

Spectral analysis shows an enhancement of spindle rate. Some cases report an increase of slow wave sleep. There is no evidence of rebound insomnia.

Zolpidem (half-life: 1.5–2.4 h)

Healthy volunteers

Standard conditions. Several studies report neither macrostructural changes with zolpidem 10 mg (Nicholson and Pascoe 1986, 1988; Terzano et al. 1988b, c, d; Terzano and Parrino 1992) nor alterations of the delta profile (Ferrillo et al. 1992). Dose-dependent variations can be observed. SL is more markedly decreased with 20 mg compared to 10 mg (Bergougnan et al. 1992), while increase of SWS is observed with doses of 20 mg and 30 mg (Nicholson and Pascoe 1986, 1988). Zolpidem 40 mg shortens REM sleep (Blois et al. 1993), and reduces k-complexes, theta and delta waves, but has no effect on sleep spindles (Blois and Gaillard 1988).

Other studies, instead, describe PSG variations even at the dose of zolpidem 10 mg, such as shortening of SL (Lund et al. 1988) and S1 (Lund et al. 1988; Scharf et al. 1988), and increase of SE (Scharf et al. 1988).

In middle-aged males, zolpidem 10 mg reduces duration of awake activity and the number of WASO in the first 6 h of sleep (Nicholson and Pascoe 1986, 1988).

In elderly volunteers, zolpidem (5 mg, 10 mg, 15 mg, 20 mg), when given randomly for 2 consecutive nights,

shortens SL and increases SE at all doses. REM sleep is slightly decreased at 10 and 20 mg. The MSLT shows no effects of the drug on daytime sleepiness (Scharf et al. 1991).

Situational insomnia. In subjects under the "first night effect" to the sleep lab, zolpidem (5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg) improves SE on each of the first 4 consecutive hours of sleep (all doses). The effect is more significant starting from the 7.5 mg dose (Vogel et al. 1988). On the same model of transient insomnia, zolpidem 7.5 mg and 10 mg decreases sleep latency, reduces the number of awakenings, and increases sleep duration (Roth et al. 1995).

In an advanced 3-h shift schedule, zolpidem (10 mg, 15 mg and 20 mg) increases TST at all employed doses, while SL is shortened only by the 10 mg and 20 mg doses (Walsh et al. 1990).

The increase in CAP rate due to acoustic perturbation, even in the absence of macrostructural modifications, is drastically reduced by zolpidem 10 mg (Terzano et al. 1988c, d; Parrino et al. 1996). The protective action of the drug is more evident on S4 and SWS. The hypnotic effect of zolpidem on sleep stability persists for at least 5 h (Terzano et al. 1988b, 1990b).

Insomniac patients

In patients with psychophysiological insomnia, a single dose of zolpidem 10 mg reduces the pathologic amount of CAP rate (Terzano and Parrino 1992), while the same dose administered for 3 consecutive nights in women complaining about chronic insomnia shortens SL and, in the first 2 h of sleep, reduces WASO and REM sleep, and increases SWS (Declerck et al. 1992).

When given for 1 week to patients with chronic insomnia, zolpidem 10 MG shortens SL, reduces TWT, and increases TST and SE. The drug is still effective after 7 nights on SL and TST, while a return to baseline values is observed upon withdrawal (Kryger et al. 1991).

When taken for 3–5 weeks, zolpidem 10 mg in chronic insomnia reduces SL, TWT and WASO and increases SE, S2 and REM sleep. Efficacy persists throughout drug administration, although the improvement is more evident in the first 10 days of treatment. Withdrawal nights are associated with a return to baseline values (Monti 1989, Monti et al. 1992; Scharf et al. 1994). Zolpidem 15 mg induces a decrease of REM sleep at weeks 3 and 4 (Scharf et al. 1994). Zolpidem 20 mg is effective in decreasing SL, REM sleep and WASO, and increasing TST, S2 and SWS (Hermann et al. 1988).

In idiopathic insomnia, a disorder which is generally treated with non-hypnotic drugs, such as tricyclic antidepressants, neuroleptics or opiates (Hauri 1994), a 2-week administration of zolpidem 10 mg improves SE at the end of the treatment period (Hermann et al. 1993).

An increase in S4 and reduced waking is found in young poor sleepers treated with a single dose of zolpidem 10 mg (Benoit et al. 1994). The same dose, when given to poor sleepers for 2 consecutive nights, reduces the number of WASO and increases S4 and SE. In addition, zolpidem decreases the theta frequencies and increases the sigma frequencies. During the first 4 h of sleep, zolpidem also increases the power in the delta bands (Benoit et al. 1991, 1992).

When given to poor sleepers on a 2-week basis, zolpidem 10 mg enhances TST and SWS and reduces SL, WASO and TWT (Oswald and Adam 1988; Kurtz et al. 1991). When administered to female poor sleepers for 15 consecutive days, zolpidem 10 mg increases SWS during the first 2 nights and S2 during the last 2 nights (Besset et al. 1990). No signs of rebound insomnia are found in the post-drug period.

In elderly subjects suffering from chronic insomnia, long-term treatment (6 months) with zolpidem 10 mg shortens REM-L (Verbeek et al. 1992), while zolpidem 20 mg improves S2, SEM sleep and SWS (Kummer and Guendel 1990).

Zolpidem synopsis

In healthy volunteers, zolpidem induces unremarkable macrostructural changes. There are reports of increase of sleep efficiency and reduction of sleep latency. MSLT: no daytime sleepiness.

In insomniacs, zolpidem increases sleep duration, slow wave sleep, and stage 2 sleep, and decreases sleep latency, intrasleep awakenings and CAP rate.

There is no evidence of daytime sleepiness (MSLT) or rebound insomnia.

Ranking of hypnotic drugs

All the hypnotic drugs are effective in increasing TST and reducing nocturnal awakenings (at least in the initial and short-term period of treatment). A brief outline of the main differences is presented here below.

Non-BDZs

Zolpidem

Short half-life; no or soft alterations on PSG macrostructure in normal sleepers, and increase of SWS in insomniacs. Reduction of the pathological amount of CAP rate. No rebound and no residual daytime effects.

Zopiclone

Short half-life; little or no modification of PSG in healthy volunteers. Increase or no change of SWS in insomniacs. Reduction of the pathological amount of CAP rate. No rebound phenomena.

BDZs

Triazolam

Short half-life as the non-BDZs hypnotics, but reported rebound insomnia. Reduction of the pathological amount of CAP rate. No evidence of daytime sleepiness (MSLT). In insomniacs, carry-over of reduced delta count after drug discontinuation.

Temazepam

Intermediate half-life: shorter sleep latencies on MSLT, but no rebound insomnia. Curtailment of SWS both in normal subjects and in insomniacs.

Flunitrazepam

Long half-life. Overall decrease of SWS both under single dose and after prolonged intake. Short-term withdrawal signs (rebound insomnia) after long-lasting treatment.

Flurazepam

Long half-life. Shortened sleep latency (MSLT). Reduction of SWS both in normal subjects and in insomniacs. No rebound phenomena. All the effects are found both under short- and long-term administration of the drug. In insomniacs, carry-over of reduced delta count after drug discontinuation.

Discussion

A number of general considerations can be drawn regarding the effects of hypnotic drugs on the architecture of sleep:

1. The great majority of the drug studies have been accomplished on young male subjects, as the use of female volunteers poses some problems. In the US, the FDA wishes women of child-bearing potential to be avoided. Yet, the use of hypnotic compounds is especially high among female and aged insomniacs.
2. When correctly used, the BDZ hypnotics potentiate sleep duration, reduce fragmentation of sleep and hasten sleep after an awakening during the night. However, BDZs not only affect sleep duration, but also the distribution and composition of the different stages of sleep (Ashton 1994; Monti 1994). In particular, most BDZs commonly used for the treatment of insomnia tend to interfere with the production of EEG slow waves during sleep (Gaillard and Tissot 1975). The reduction of slow wave sleep can be detected both under visual scoring (in the form of decreased stages 3 and 4) and under automatic analysis of the power spectrum (in the form of a reduction in the delta band frequencies and slow wave activity). Especially after repeated administration of BDZs, both in normal sleepers and in insomniacs, slow wave sleep is drastically curtailed and is slowly restored only after discontinuation of the treatment. Accordingly, a reduction in the delta band frequencies appears immediately after the beginning of medication, persists with intermediate and long-term administration, and continues after withdrawal. It is interesting to note that these effects on EEG parameters are independent of the kinetic properties of the investigated drug. In fact, the depression of SWA occurs with short-, intermediate- and long-acting BDZ compounds. The recent introduction of hypnotic agents that enhance (or at least do not alter) EEG synchronization during sleep has been greeted with interest. Among these compounds, the novel hypnotics with a non-BDZ molecular structure, specifically the imidazopyridine zolpidem and, to a lesser degree, the cyclopyrrolone zopiclone, can be classified as more "natural" agents as they provide protection to sleep without interfering with its normal structure. The "ecological" properties of these compounds have been attributed to their high selectivity for the GABA macro-molecular complex. In particular, zolpidem shows an impressive affinity for the ω1 receptors (Langer et al. 1988).
3. The discontinuation of both short- and long-acting BDZs, administered to chronic insomniacs over consecutive weeks, may result in similar sleep patterns such as persistent decrease in the delta count (Johnson et al. 1983). Thus, the kinetic properties alone cannot entirely explain the carryover effects and the EEG changes that occur when the drug is discontinued.
4. All BDZs can induce rebound insomnia and withdrawal phenomena on cessation of BDZ intake may supervene, both in normal subjects and patients with insomnia, even after low dose administration (Kales et al. 1978; Nicholson et al. 1980; Ashton 1994). Rebound insomnia can be especially experienced during the discontinuation of short- and intermediate-acting BDZ hypnotics. Promising findings seem to emerge, instead, from the use of non-BDZ hypnotics. No rebound effects on sleep duration and architecture are reported when zopiclone and zolpidem are abruptly discontinued.
5. Long-acting BDZs shorten sleep latency on the MSLT the day after bedtime administration. In contrast, no residual effects are reported when hypnotics with a short elimination half-life are used.
6. Literature offers a number of models of situational insomnia in healthy subjects: the use of noise delivered either continuously (Terzano et al. 1990a) or intermittently (Okuma and Honda 1978), the accomplishment of sleep during the daytime hours (Nicholson et al. 1980; Walsh et al. 1984; Traschel et al. 1990; Kanno et al. 1993), the exploitation of the "first night effect" to the sleep laboratory (Roehrs et al. 1990). These models are used to assess the protective effect of a hypnotic drug in normal subjects exposed to a standardized condition of situational insomnia. The use of a controlled perturbation in heal-

thy subjects allows determination of a condition of situational insomnia unbiased by any mental interference. International authorities and registration boards actually recommend to privilege "active methods" on healthy individuals in the studies of hypnotic drugs. In particular, the GIENS Report issued by the French Ministry of Health, suggests that active means of controlled sleep disturbance should be included in trials of efficacy of hypnotic compounds in subjects who are good sleepers (Kurtz and Sauvanet 1988; Kurtz et al. 1991).

7. Due to the great sensitivity of sleep microstructure in detecting even slight external or internal perturbations, all baseline sleep recordings should be carried out in a sound protected environment. In order to assure a physiological sleep, the World Health Organization (1980) recommends that the sound pressure level should never exceed 35 dBA. Accordingly, the normative values of CAP rate refer to acoustic conditions below 30 dBA (Terzano et al. 1986, 1988a, 1990a). In healthy adults without complaints about sleep, a sound pressure level of at least 45 dBA determines a significant enhancement of CAP rate that correlates with a poor sleep quality even without concomitant macrostructural changes (Terzano et al. 1988c, 1993). The variations of CAP rate in this framework of acute situational insomnia have been exploited to investigate homogeneous samples of subjects with a common sleep disturbance and assess against this background the hypnotic effects of drugs. Indeed, the term "insomnia" may cover clinical entities that differ widely in respect of age, duration, clinical state, and pharmacological history of the patient. These complex issues make the recruitment of appropriate patients for treatment studies particularly difficult. The comorbidity in insomniac patients for mental disturbances or other sleep disorders may also confound the clinical approach. Although any extrapolation from normal individuals to clinical cases must be always carried out accurately, it is interesting to notice that all the neurophysiological premises collected in the "healthy volunteers" domain were confirmed in the "patients" domain.

Final considerations

From the analysis of the PSG studies presented in the present review some suggestions for further investigation are proposed:

(a) Although considerable information regarding the efficacy of these drugs in the treatment of transient insomnia is available, less is known about the maintenance of drug effectiveness, the possibility of dependency and other adverse consequences with prolonged use of hypnotic agents. Neuropsychological studies report that the long-term use of BDZs is not only responsible for significant cognitive impairment (Golombok et al. 1988), but lack of cognitive recovery can persist following withdrawal from enduring BDZ administration (Tata et al. 1994). Whether the structure of sleep is also impaired when BDZs are taken for lengthy periods and after discontinuation remains an open question.

(b) Emphasis is generally put on the need to suspend the administration of hypnotic drugs 3–4 weeks after the start of treatment. However, the current prevalence of chronic forms of insomnia generally forces to extend their periods use, especially when other forms of treatment appear impracticable or ineffective. The intermittent use of hypnotic drugs may represent a valid therapeutical compromise when the individual suffers frequent bouts of insomnia. Unfortunately, no adequate PSG studies are available on this therapeutical procedure.

(c) The information provided by conventional parameters tends to oversimplify the nosographic classification of insomnia as well as the hypnotic properties of drugs. Accordingly, the polysomnographic measures are *not* required by the International Classification of Sleep Disorders (Thorpy 1990) for the diagnosis of sleep disturbances. As a result, alternative non-PSG methodologies are increasingly used to measure sleep, e.g. questionnaires, actigraphy. Whereas these techniques can be recommended for screening purposes in the diagnosis of insomnia, the priority of PSG method is re-established when more accurate information is required. For example, REM sleep can be the critical site of intra-sleep awakenings in some insomniac patients (Gaillard 1990). In this case, the assessment of REM sleep fragmentation and the eventual drug action can be monitored exclusively with the support of PSG measurement.

(d) Whereas the literature especially stresses the ability of hypnotic drugs to reduce intrasleep awakenings and to prolong total sleep time, the relationship between hypnotic drugs and the structure of sleep, in particular stages 3 and 4, frequently remains ambiguous and incomplete. To state that a particular BDZ, when administered to insomniac patients (in whom there is evidence of deep sleep reduction), preserves the sleep structure as SWS remains unmodified, neglects a crucial shortcoming of the drug. Similarly, it is claimed that BDZs do not interfere with the physiological architecture of sleep since they retain the cyclic alternation between NREM and REM sleep, although there is evidence of a serious downfall of SWA (Borbely et al. 1983; Borbely and Achermann 1991). If a hypnotic agent significantly alters the amplitude of slow wave activity it certainly affects the whole sleep structure, thus interfering with the basic mechanisms that modulate EEG synchronization (Borbely 1994). It is unknown whether the changes in sleep stage occurrence and distribution have any relevance on health, illness or psychological well-being. In any case, the ability of a drug to guarantee a sleep profile which approximates most closely the physiological micro- and macrostructure of sleep, should be ranked among the fundamental characteristics of an ideal hypnotic compound.

(e) Hypnotic drugs are known to induce variations in the phasic events of sleep. BDZs, in particular, increase the extent of spindles and reduce the number of k-complexes, slow waves and EEG arousals. According to the 1992

report from the American Sleep Disorders Association (ASDA), an EEG arousal is an abrupt shift in EEG frequency, which may include theta, alpha and/or frequencies greater than 16 Hz but not spindles (American Sleep Disorders Association 1992). Although several contributions support the arousal-related function of k-complexes and delta waves (Loomis et al. 1938; Roth et al. 1956; Church et al. 1978; Halasz and Ujszaszi 1991), the ASDA report states that these phasic events cannot be scored as arousals. Both fast and slow EEG phasic events are instead incorporated in the CAP framework and referred to a condition of arousal instability. Although it is labor intensive, the visual scoring of CAP has provided integrative PSG information for the diagnosis of several sleep disorders and for monitoring the effects of hypnotic drugs on sleep (Terzano and Parrino 1993). The role of CAP, especially in pathological states, is currently the subject of considerable study (Cooper 1994). The encouraging perspectives that emerge now from the automatic scoring of CAP (Ferrillo et al. 1994; Rosa et al. 1994) move in the direction of a drastic abatement of the time costs and lay the bases for a more extensive application of this method.

(f) Persons over 65 receive hypnotics disproportionately more than younger ones. Thus, the possibility to have highly sensitive PSG measurements is important for studies in elderly subjects in which the macrostructural alterations due to physiological aging are hardly distinguished from the sleep changes induced by hypnotic drugs among the younger population.

In conclusion, we believe that although PSG investigation is demanding, it is an essential means for investigating sleep. In effect, PSG assessment now is required by the US Food and Drug Administration for measuring the hypnotic effects of any compound being submitted for approval (Roth et al. 1994).

PSG provides objective measurement of sleep structure and documents drug efficacy on sleep induction and maintenance. The availability of additional highly sensitive PSG parameters candidates this laboratory tool to an even more pivotal role for evaluating the effects of drugs on the sleeping brain.

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