Benzodiazepine therapy

KEYWORDS: Drug Therapy; Benzodiazepines; Drug Dependence; Physician-patient Relations; Family Practice.

THE status of benzodiazepine therapy today lacks definition. It has been popularly described, both as the Universal Panacea for the 20th Century Malady and simultaneously as a dangerous drug.

"Concern regarding the continued efficacy and hazards of benzodiazepines during long term treatment has led the Food and Drug Administration of America to mandate caution against anxiolytic treatment of more than four months duration".[1]

The doctor can prescribe the drug in order to avoid becoming involved with the patient.

A global approach however, with an awareness of critical and complex interactions at play between the drug, the doctor and the patient, is mandatory if one is to be able to predict, in a rational manner, those situations which are high risk for abuse of the drug.

There are definitive areas of medical experience which are extremely difficult to prove in terms of tabulated scientific data or comparative methodology. This is especially pertinent when one is dealing with a subject as delicate as the psyche of a patient, his inner, private conflicts and his attitudes towards life, his family

and himself. His response, for example, to medication in terms of ill-defined changing parameters of mental attitudes and priorities can be measured by his physician only in terms of the physician's previous experience and intimate knowledge of the patient, which has been acquired, usually, through many years of involvement with his patient through various crises and developmental growth cycles.

I feel, therefore, that there is a contribution to be made by the formal consideration of certain observations and conclusions drawn from the contemplative study of benzodiazepine usage and abuse, free from the rigidity of academic restrictions such as double blind trials. Much is therefore impressionistic and philosophical.

Abuse of benzodiazepines is not purely a function of the neurotic patient, but is also due to the effect of the drug and the irresponsible prescribing habits of the physician.

"In the past three years, there has been a dramatic change in medical attitudes to the prescribing of benzodiazepines. Before 1980 these drugs were regarded as not only safe and effective anti-anxiety drugs and hypnotics, but also free from important unwanted effects. Since then there has been rising alarm about the risk of pharmacological dependence after regular consumption of the drugs".[2]

If benzodiazepines are used for any length of time for psychological indications, the condition for which the drug is being used does not resolve, but in the absence of supportive psychotherapy, deteriorates.

The observations are not intended to detract from the benefits which may be accrued from the benzodiazepines in selected situations, under supervised and responsible use. Rather, they are intended to highlight the dynamic inter-relationship which exists between the drug, the prescribing physician and the personality profile of the patient. They are also intended to stress the immorality of irresponsible prescription.

With the apologetics disposed of, let me introduce two basic hypotheses:

i. That the abuse of benzodiazepines is not purely a function of the neurotic personality type of the patient, but is also due to the exceptionally effective primary response and mood-elevating effect of the drug, together with the irresponsible prescribing habits of the physician, who utilizes the drug's excellent initial response profile as a protective barrier for himself, in order to avoid the time-consuming alternative of involvement, with supportive psychotherapy. His subsequent failure to assume responsibility for his compromised patient, once he is enslaved by the drug, positively re-inforces the tendency to abuse.

ii That, paradoxically, if benzodiazepines are used for any length of time, for psychological indications, the condition for which the drug is being used, usually does not resolve, but, in the absence of supportive psychotherapy, deteriorates. A regression of the patient's symptoms occurs, with the development of additional iatrogenic symptomatology in those very areas of his psyche which were compromised in the first instance, and which prompted the initiation of benzodiazepine therapy. A sequence of predictable events, the vicious cycle of benzodiazepine usage is set in motion.

Real life situations highlight the paradox between the expected effect of the drug and the actual results experienced.

To support the validity of the first part of the hypothesis, I shall discuss, in turn, the characteristics of the drug, the characteristics of the prescribing physician and the characteristics of the patient. It is the dynamic interrelationship between these three critical variables, and not any single factor in isolation, which is responsible for the unfortunate status of benzodiazepine therapy today.

To support the validity of the second part of the hypothesis, I shall highlight situations in which the paradox between the expected effects of benzodiazepine therapy and the actual results of therapy is often observed.

1. CHARACTERISTICS OF THE DRUG

Benzodiazepine derivatives are all closely related chemically, but vary in very subtle ways, both in their biochemical and metabolic behaviour, as well as in their clinical actions and reactions. Many of these differences do not seem to be appreciated by the prescribing physicians, if one rationalises their choice of benzodiazepine with its pharmacokinetic clinical indication.

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The subtle ways in which the derivatives of benzodiazepine differ in their biochemical and metabolic behaviour, should be very clearly understood.

The benzodiazepine derivatives have differing sedative and hypnotic properties, differing serum half-lives, differing muscle-relaxant properties, differing side-effects and differing dosage profiles. Without a practical working knowledge and rational application of their individual differences, both biochemical and physiological, rational decisions regarding the correct arena of usage will be impossible.[3]

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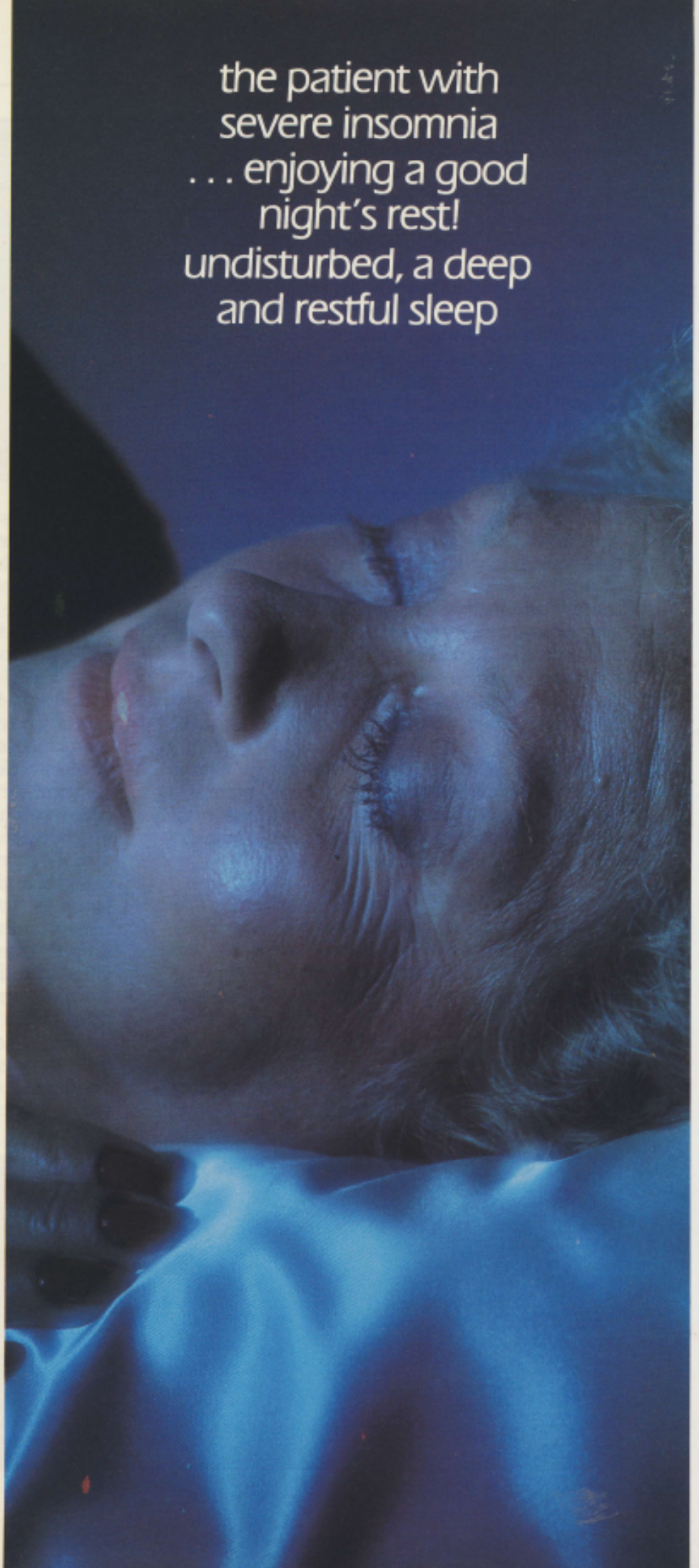
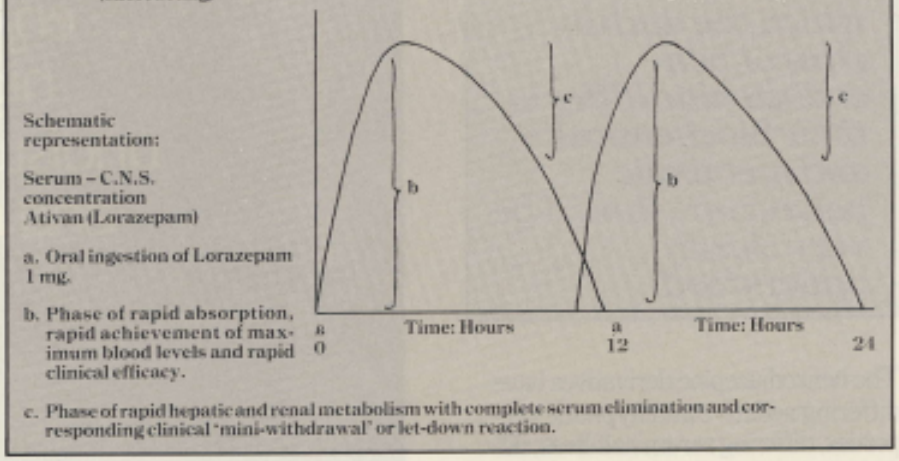
Consider the absurd situation where Nitrazepam (Mogadon) which, together with its active metabolites, has a half-life of 30 hours, is used, and, in fact freely advocated, as an Hypnotic, to induce and maintain sleep. Ostensibly, no thought is given to the high serum levels present during the subsequent day, when, if



a sleep-disturbance is the only manifestation of an anxiety-related or depressive disorder, one would hope to be clear-headed and alert. In this situation, a rational decision would be to use, rather, a derivative which is metabolised in a shorter time, corresponding with the time during which one wishes to sleep, with a clearance of active metabolite from the serum during the following day. In this situation Oxasepam (Serapax) or Lorazepam (Ativan), with serum half-lives of between 6 to 12 hours, would surely be the rational choice? Straughan, in his article *Which Benzodiazepine, Why and How,* emphasizes these aspects.[3] In practice, however, these new-generation rapidly metabolised benzodiazepines have been marketed predominantly for chronic free-floating anxiety, or the situational disturbance, where, paradoxically, constant, unfluctuating 24 hour serum levels are mandatory. Surely a long-acting drug such as Diazepam (Valium: Roche) which, together with its active metabolites, has a serum half-life up to 90 hours, but with significantly lesser hypnotic properties to Nitrazepam would be the rational choice in these cases?

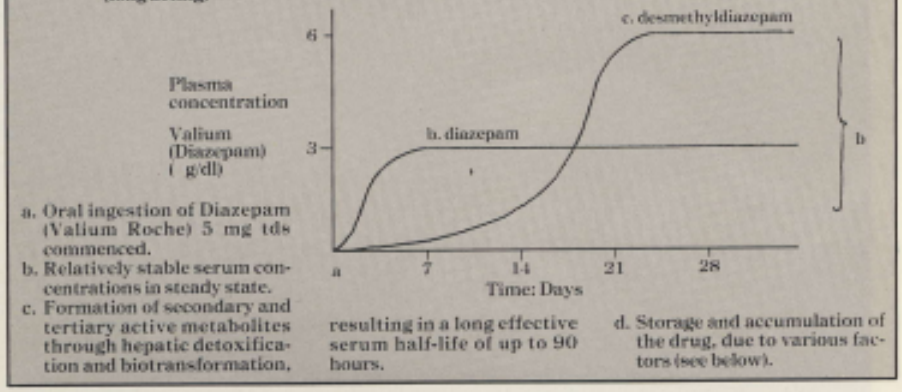
FIGURE I: Serium level profile – Lorazepam (Ativan) at 1 mg/12 hourly (short acting)



A brief examination of the blood serum level profiles of both a short acting benzodiazepine, such as Lorazepam (Ativan), taken at a dosage of 1 mg bd and a long acting derivative such as Diazepam (Valium) taken at 5 mg tds, will show important differences.

We observe the tendency for marked diurnal serum fluctuation of Lorazepam at this bd dosage. The extremely quick achievement of maximal serum levels, which is even quicker if the tablet is allowed to dissolve sublingually, has its clinical counterpart in the rapid alleviation of symptoms, the favourable mood-elevating effect and the general efficacy of this, and similar preparations. The equally rapid elimination from the serum has its clinical counterpart in the development of a 'mini-withdrawal' or 'let-down' phase, during which time the patient experiences his anxiety provoked symptoms in an exaggerated manner, due to the rapid transition from a protected psyche by virtue of his high serum levels of Lorazepam, to an unprotected, vulnerable state. It is this feature of the high peaks and the low troughs with some of the short acting benzodiazepines when the dosage is not adjusted according to the pharmacokinetic profile of the drug, which I believe to be one of the major contributors to the rapid development of patient dependence. As Straughan confirms "because lorazepam has no tendency to accumulate, on abrupt withdrawal of the drug there is a sudden decline of plasma and tissue levels, such as is experienced, for example, with ethanol. Thus if a person has been receiving lorazepam for any length of time, and is dependent on the drug for its anti-anxiety effectiveness, abrupt withdrawal must on pharmacological grounds, be expected to give rise to withdrawal problems".[3] It is during the 'mini-withdrawal' phase, when his anxious symptoms break through the rapidly falling blood levels of the drug, that the patient frantically ingests his next tablet, often before the next dosage is due. The rapid absorption and effect again are remarkable in their alleviation of symptoms. It does not take long for this cycle to become fairly ingrained in the patient's daily routine, and the ingestion of ever increasing amounts of the drug reflect the development of a Pavlovian conditioned response to even the most innocuous of daily situations.

FIGURE II: Serum level profile – Diazepam (Valium at 5 mg tds 8 hourly) (long acting)[3]



The patient becomes obsessive about the availability of the drug, and rapid dependence, mega-dosage and tolerance produces a guilt-ridden and vulnerable patient.

The key to the development of a more stable patient response to a short acting benzodiazepine such as Lorazepam would include:

i. Knowledge and application of its pharmacokinetics and half-life with the re-adjustment of dosage to tds or qid levels to ensure a more stable

Benzodiazepine therapy

serum level. The phase of rapid elimination will then be less marked, and the mini-withdrawal effect will be negligible.

ii Selection of the patient, excluding those of a highly neurotic and dependent personality type, who would be more prone to develop dependence as described above (See Characteristics of the Patient). Straughan again concludes that "because of its considerable sedative action at the dosages usually employed, lorazepam is frequently prescribed for those persons whose anxiety levels are high, and who are then the very candidates to feel anti-anxiety agent withdrawal effects more acutely and extensively than less neurotic or less anxious persons".[3]

By consideration of the serum blood levels of a long-acting benzodiazepine, we see immediate important differences to the short-acting profile as represented by Lorazepam.
Once stabilisation between absorption, storage and elimination has occurred (which in the case of Diazepam takes about 7-10 days) a steady state is reached, provided that cognisance is taken of the quality of the patient's liver, dosage readjustment is instituted and usually reduced, and the patients are followed up to assess possible accumulation and toxic effects. In geriatric patients with hepatic dysfunction, Lorazepam, with no active metabolic by-products, is preferable.

There is no profound variation in serum levels of Diazepam on a daily basis; thus the peaks and troughs are smoothed out. Mini-withdrawal, let-down, and the consequent breakthrough acute anxiety reactions are not as frequent. The smooth, consistent blood levels of Diazepam without the diurnal breakthrough reactions help to detract from the importance often attached to the act of ingestion of a tablet. The ingestion of Diazepam 5 mg does not have as dramatic a clinical effect if taken against a stable blood-level of the drug as the ingestion of Lorazepam 1 mg would have.

It has been observed that once a benzodiazepine has been given for a certain period of time, a degree of tolerance develops.

Another important consideration in benzodiazepine therapy is the understanding of the phenomenon of tachyphylaxis. This interaction between the patient and his medication is not peculiar to the benzodiazepines, but is observed in therapy with many other classes of medication, including the Beta Sympathomimetics (e.g. Salbutamol) and the non-steroidal anti-inflammatories (e.g. Indomethacin, Oxyphenbutazone). An understanding of tachyphylaxis is a pre-requisite for the development of a rational approach to therapy, particularly where problems such as incremental dosage regimes, dependence and abuse become manifest. It has been observed that once a benzodiazepine has been given for a certain period of time, a degree of tolerance develops, necessitating higher and more frequent dosage to overcome the same anxiety-provoking situations as before (in the case of benzodiazepine therapy). It seems that the troubled psyche has gradually and subconsciously acquired the strength to climb out, over and above the protective barrier offered by the existing blood levels of the benzodiazepine, to effectively establish a new, higher threshold level of anxiety, which breaks through the existing dosage regime with increasing frequency until the dosage is either increased, or the sub-type of benzodiazepine is changed to a different derivative.

This explains the severe acute anxiety reactions as observed in many patients who are currently taking benzodiazepines, and must be understood if the paradox as stated above concerning the apparent deterioration of a patient's symptoms while on benzodiazepine therapy, is to be understood. If tachyphylaxis, with the breakthrough of acute psychosomatic symptomatology happens to coincide with the phase of rapid elimination of a short acting benzodiazepine such as Lorazepam (see Fig. 1) with a mini-withdrawal episode, the clinical reaction can be devastating, with complete destabilisation of the patient's condition.

I have hoped to show, in the above considerations, that a thorough working knowledge of the various pharmacokinetic and clinical parameters of the benzodiazepine derivatives is mandatory if one is to be efficient at being of assistance in helping those of our patients who, in spite of adequate psychotherapy and counselling, need to be on a benzodiazepine for varying periods of time.

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