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Differential Psychopharmacology of Anxiolytics and Sedatives

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J.-R. Boissier, Romainville

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Clinical Differences between Anxiolytics and Sedatives

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Introduction

Anxiety and its manifestations are inherent to human life. Normal anxiety acts as a warning signal for the mind as does pain for the body. When anxiety and its various manifestations reach a degree where human functioning is hampered, it then becomes pathological and some form of treatment may be required. The anxiety threshold can vary between individuals, as it does for physical pain, and differ between cultures. Anxiety, depending upon its intensity, does not have only negative, disintegrative facets, but has also positive, constructive ones. Indeed, at a low level, it can help with the mastery of the environment, lead to better efficiency, to creative activity and success. Anxiety can be alleviated either by psychological or pharmacological means, or by a combination of both. Drugs used to produce anxiolysis have received various names, such as tranquilizers, sedatives, anxiolytics, ataractics. In addition, other types of psychotropic drugs possess, to various degrees, some kind of so-called sedative, anxiolytic effect, although their main clinical property is rather to treat thought or mood disorders, such as schizophrenia or depressive states, Therefore, from a clinical viewpoint what is the meaning of sedative action, of anxiolytic action, and is there a practical difference between them? Before discussing however the eventual clinical differences between sedative and anxiolytic actions, it is important to consider briefly anxiety and its nature.

Anxiety and its Nature

Anxiety is a complex reaction not easily conceptualized (35). It has many facets and unfortunately only some highlights can be presented here. Anxiety is

an emotion encountered all through life and in all types of human conditions. It has been defined as a feeling of disarray experienced during the poignant expectation of impending danger (12). It has also been defined as an emotion, usually unpleasant, which has, subjectively, the quality of fear or of closely related emotions (36). Anxiety may interfere with thinking processes and concentration. If a feeling of impending danger is implicit in anxiety, there is however no recognizable threat, or if the threat exists it is, by reasonable standards, disproportionate to the emotion seemingly evoked. The level of anxiety can range from uneasiness to full-blown panic accompanied by the physical concomitants of fear. Although anxiety is common in the population, its exact incidence is difficult to estimate because it is, as already stated, a highly subjective feeling as is physical pain, and tolerance of it varies greatly. A number of psychological tests of varying reliability and validity can measure anxiety.

Before Freud, others like Kierkegaard had recognized the importance of the phenomenon of anxiety in understanding human behavior. Freud however first attempted to explain anxiety and its manifestations in scientific terms and tried to focus the attention on anxiety as a basic element for the understanding of emotional disorders. He elaborated a theory which he continued to modify throughout his life (4, 40).

Freud considered that anxiety had an inherited biological basis which endowed the human organism with the capacity for reacting with the psychological and physical manifestations of anxiety, and he endeavored to explain the place and importance of anxiety in mental life (4). The main difference between Freud and Kierkegaard lies in the fact that, while for the former anxiety had biological roots and could be comprehended in terms of natural cause and effect processes, for the latter it constituted a manifestation of human freedom (50).

For Kierkegaard, father of the existential dialectic, man will become what he chooses to make of himself. He has the freedom of choice between an authentic or an inauthentic mode of existence and will suffer the ideal of despair and existential anxiety if he opts for the authentic mode of existence (11). The phenomenologic and existential concepts have strongly influenced contemporary psychiatry and its conception of life situations with respect to anxiety (55). Contemplated from a biological standpoint, anxiety has therefore a biological foundation and acts as a signal of impending danger (4, 44) triggering emergency control measures (43). Anxiety has also been studied from the learning theory viewpoint in terms of secondary drive, as a source of secondary reinforcement and of conditioned fear response (13).

For his part, *Pöldinger* (42) aiming at a practical assessment of anxiety, in view of its treatment, has schematized the concepts of *Binder* (2) and *Kielholz* (29) concerning its genesis. He has distinguished the following different types of anxiety: real, vital, conscious, neurotic and psychotic. Real anxiety of fear arises from an environmental threat and is a warning signal of a real danger. It is

necessary for the defence of the entireness of the individual and should therefore not be eliminated by drug treatment. Vital anxiety accompanies somatic diseases, for instance an infarct, induces the protective reaction of seeking proper care and requires treatment only if it persists to the prejudice of physical recovery. Conscious anxiety is an integrated feeling originating from the environment, belongs to normal psychology, constitutes an intrinsic part of the culture and is often difficult to differentiate from neurotic anxiety. Neurotic and psychotic anxieties (the former including free-floating anxiety) are the two types, in addition to intense conscious anxiety, that need treatment and they represent the really pathological types of anxiety. These last two types of anxiety, neurotic and psychotic, must be kept in mind not only for drug treatment, but also for psychotherapy (16).

A last distinction between types of anxiety has been made between state anxiety and trait anxiety (35, 36, 39). State anxiety is related to anxiety felt at a given moment in a particular situation, whereas trait anxiety refers to the habitual inclination to be anxious over extended periods of time. State anxiety can be superimposed on trait anxiety. The individuals affected with trait anxiety possess a lowered threshold for experiencing this feeling in a wide diversity of situations perceived as threatening. Obviously, the results of treatment, when necessary, may vary in these two types of anxiety. Finally, anxiety may be sustained, but more often is episodic and can last from a few minutes to hours or days (39). There is no agreement as to whether anxiety states form a discrete homogeneous syndrome.

This complexity of the nature therefore renders the evaluation of potential therapeutic agents against anxiety quite difficult, both in animals and in humans.

The Semantic Problem

The problem of discussing the clinical differences between anxiolytics and sedatives resides, to some extent, in the looseness of utilization of these terms from a clinical standpoint and this creates semantic difficulties.

The fact that the application of the term 'sedative' to the group of substances that include various depressants of the central nervous sytem such as the hypnotics (barbiturates and non-barbiturates) and other compounds such as many antihistamines and centrally active anticholinergic agents, is somewhat misleading had already been acknowledged for some time. Indeed, the principal use of these miscellaneous substances was considered to be the production of drowsiness (51). *Sharpless* (51) has emphasized that the term 'sedative' remained from the era when the sedative-hypnotic compounds were the only drugs (apart from alcohol, opiates and belladonna) available to calm anxious and disturbed patients. With the discovery and development of modern psychotropic agents,

the drugs traditionally described as sedative-hypnotics have of course come to play a lesser role in daytime sedation (22).

In the literature, unfortunately, there is too often an interchangeable use of the qualificatives–sedative, anxiolytic. It has been pointed out in recent years that the terms 'hypnotic', 'sedative', 'soporific' and 'tranquilizers', were used to characterize a large group of central nervous system-depressant drugs and that these terms had been utilized so often interchangeably that many physicians had come to consider them synonymous (19).

Discussing the nomenclature of psychotherapeutic drugs, *Hollister* (24) explained that the epithet 'tranquilizer' became preferred because the term 'sedative' had become a discredited word among psychiatrists after the belated finding that barbiturates could induce physical dependence. He stated that the implications of these two words were nevertheless the same and that the adoption of the term tranquilizer had led to the assumption that the drugs so labeled constituted newer types of sedatives. He felt that this could be true to a certain extent for the drugs used for the treatment of anxiety. He suggested that a more realistic nomenclature, based on the putative clinical use of the psychotropic drugs, be utilized. He therefore labeled antianxiety drugs those used for the management of anxiety, antipsychotic drugs those for the treatment of schizophrenia and other psychoses, antidepressant drugs those for treating depression and antimanic drugs those for the treatment of mania. He realized the limitations of his nomenclature recognizing that, under certain circumstances, each of the drug types could be used for other purposes. In looking at his nomenclature, it appears that the term 'antipsychotic' mostly linked to the treatment of schizophrenia (antischizophrenia agent) is slightly misleading in the sense that antimanic and antidepressant drugs are also used for the treatment of affective disorders of psychotic intensity.

For their part, *Klein and Davis* (32) had correctly pointed out earlier that the term 'minor tranquilizer' was very unfortunate since it implied that these drugs acted like major tranquilizers, but to a lesser degree, being thus less potent. They commented that it could therefore be expected that large doses of minor tranquilizers would produce the same clinical effects as major tranquilizers administered in small doses and also be effective in a similar range of clinical conditions. They suggested that psychotropic drugs should rather be defined as specific drugs for specific purposes. Recently, *Klein* (31) underlined that growing clinical experience had finally led to revising the drug terminology as *Hollister* proposed, the terms 'antipsychotic' and 'antianxiety agents' having replaced those of major and minor tranquilizers, indicating thus a qualitative distinction in targets and mode of action of these agents.

A widely used classification of psychotropic drugs is the one elaborated by *Delay* (6, 7, 8) and *Deniker* (9, 10). This classification has the merit of a clear definition of the terms coined and is not subjectively tainted by the meaning of

terms whose significance has become imprecise and misleading. Their classification differentiated psychotropic drugs as follows: (i) psycholeptics – hypnotics, tranquilizers and neuroleptics, (ii) psychoanaleptics – thymoanaleptics, nooanaleptics and other stimulants; (iii) psychodysleptics – hallucinogens and oneirogens.

The psycholeptics depress the psychic activity and, because of their antimanic action, the lithium salts which act as 'thymoregulators' (56) were included later in this category. The hypnotics act preferentially on sleep function and are obviously used for the treatment of sleep disorders. The neuroleptics are characterized by their predominant action on psychomotor functions, and by their efficacy against schizophrenia and other psychotic disorders. The tranquilizers, used against anxiety and emotional tension, do not possess any antipsychotic property, but mainly an anxiolytic one. However, hypnotics and neuroleptics, at lower doses, can overlap in their action of that of the tranquilizers and produce similar effects. The pyschoanaleptics stimulate the psychic activity and include substances acting on the mood (thymoanaleptics), the antidepressants, or on the vigilance (nooanaleptics) such as the amphetamines. The psychodysleptics perturbate the psychic activity and refer mainly to the various hallucinogens and oneirogens. Due to its clarity, this classification, grouping the various psychotropic drugs by their main action on the mind, will be used in the next portion of this paper.

Animal Psychopharmacology

In animal psychopharmacology, the majority of the tests used to screen potential psychotropic agents and to detect their eventual therapeutic properties have no or little relationship with human mind and clinical situations.

The activity spectrum of the various types of psychotropic drugs has been clearly summarized by *Boissier and Simon* (3) within the frame of the classification of *Delay and Deniker,* as well as the various tests utilized to detect and objectify their activity – their pharmacological profile. Pharmacological criteria have also been described for the classification of various psycholeptics (18, 33, 53). The pharmacological characteristics in animals of the main classes of drugs used as psycholeptics in man will not be discussed in detail here.

It suffices to mention that the sedative action of the neuroleptics is quite different from the one of hypnotics. At usual dose range the neuroleptics will not induce sleep and influence very little the respiratory center. They do not paralyze the central nervous system functioning, but only lower its tonus. This pharmacological property is shown mainly by a reduction of the spontaneous motor activity, by an inhibition or disappearance of fear and by a loss of the conditioned responses. Three main properties used to screen potential neuro-

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leptics is their capacity to induce catalepsy, their antiapomorphine activity and their protective action against amphetamine group toxicity in mice. Catalepsy is the reflection of their typical clinical side effects, that is the production of extrapyramidal symptoms.

With respect to tranquilizers, they differ from the neuroleptics both qualitatively and quantitatively. Like the neuroleptics, they are different from the hypnotics as they do not induce sleep at usual dose range. Unlike the neuroleptics, they do not provoke catalepsy or any other extrapyramidal symptom and have no direct action on the neurovegetative functions. They share with the selective inhibitors of interneuronal transmission and with the myorelaxants the property of blocking the medullar polysynaptic reflexes, thus inducing muscular flaccidity and ataxia. However, at high doses, they can also inhibit the conditioned reflexes. Most tranquilizers also possess some anticonvulsive effect and exert an evident taming effect without sedation.

Three main properties used to screen the potiential tranquilizing agents–sedation, neuromuscular relaxation and anticonvulsant activity–have recently been criticized with respect to their relevance to humans (52). Indeed, sedation and neuromuscular relaxation are two properties responsible for undesirable side effects in man, and it was felt that the anticonvulsant activity might explain convulsions occurring sometimes upon withdrawal of these agents. Therefore, in animals, three undesirable side effects constitute the main basis for screening potential tranquilizers and in humans, the efforts made to objectify the effects of the tranquilizers have mostly studied side effects or undesirable reactions: effect on vigilance, on sleep, etc, (52). Another screening test that also has little relevance in man, except for the prediction of eventual drug interactions, is the potentialization of the effects of alcohol, barbiturates and analgesics.

Some Neurophysiological Aspects

From a neurophysiological viewpoint, the various types of drugs used to obtain sedation, anxiolysis, such as hypnotics, neuroleptics and tranquilizers have different sites of action in the brain (42). The barbiturates decrease the excitability of the reticular formation and the neuroleptics, like chlorpromazine, elevate its excitatory threshold, thus attenuating afferent stimuli. At usual dose range, the tranquilizers inhibit some thalamic nuclei and the limbic system, the benzodiazepines acting preferentially on the latter, mainly on the hippocampus (49). Clinically, it has been shown that a barbiturate (amylobarbitone sodium) compared to a benzodiazepine (chlordiazepoxide), at doses equivalent for the relief of anxiety, had a greater hypnotic effect, thus demonstrating some differences between these two types of drugs (41).

The various classes of psychotropic drugs that can be used to induce

sedation, anxiolysis, provoke particular changes in the wake EEG, as well as typical modifications on the evoked potential and on sleep pattern. According to *Saletu* (48), in man, for instance, the tranquilizers generally provoke in the wake EEG an increase of beta activity, as do barbiturates, and an augmentation of average frequency, as well as a diminution of alpha activity, of the average absolute amplitude, of the dominant frequency and of the epileptic grapho-elements. For their part, the neuroleptics induce an augmentation of delta waves, of theta waves, of the amplitude, of the synchronization and of the epileptic grapho-elements, as well as a decrease of beta waves, of the average frequency, of the frequency deviation and of the dominant frequency.

Sedative vs. Anxiolytic Action

The difficulty of establishing clinically a clear-cut distinction between the tranquilizers and the other drugs also used at various doses for anxiolysis, such as the neuroleptics and the hypnotics, has long been acknowledged. *Deniker* (10) believed that the tranquilizers could be defined mainly by differential comparison with the neuroleptics and the hypnotics. For his part, *Ginestet* (17) already stressed at the time that the differences in the indications and the therapeutic efficacy of the various classes of psycholeptics represented a challenge that went beyond a semantic dispute. *Lehmann* (37) felt that the tranquilizers were characterized by their effect on emotional tension, that they had no major therapeutic action on psychotic manifestations, and that their therapeutic values laid essentially in their anxiolytic effect when employed in neurotic conditions. He thus pointed out that ideally a true tranquilizer should specifically reduce the level of anxiety, or, more generally, of emotional tension, without inducing drowsiness or sleep. He also compared the differences and similarities of the psychopharmacological action of the sedative-hypnotic drugs, of the tranquilizers and neuroleptics, underlining at the time that no simple criteria at the behavioral level allowed reliable distinction between these drugs, although at the pharmacological level the differences were clearer.

According to *Jaffe* (25), at lower doses, the sedative-hypnotic agents share the common property of producing a type of reversible general depression of the central nervous system which is associated with feelings of relaxation and drowsiness, whereas at slightly higher doses, they can induce sleep. He also commented that until recently the common belief had been that no clear distinction existed between tranquilizers and sedative-hypnotic drugs, and that proper adjustment of the doses could induce the desired effect–anxiolytic, sedative or hypnotic. However, he reminded that this implied that, despite their different chemical structures, all these drugs most likely acted in a similar way, but that some studies had suggested that differences may exist, qualitative and quantit-

ative; namely, between barbiturates and benzodiazepines. Finally, some researchers have expressed the opinion that the utilization of the barbiturates, and by extension of the related sedative-hypnotics, was obsolete (34). Some feel that their use should be restricted to the treatment of insomnia and that even there, certain benzodiazepine derivatives, such as flurazepam, are superior to them (26, 27, 28).

For the treatment of neurotic anxiety, the benzodiazepines represent safe and effective agents, and it is indeed extremely difficult to commit suicide with them (20, 21, 24, 47, 52). Various classes of psychotropic drugs, other than the tranquilizers, show some efficacy in the treatment of neurotic anxious syndromes, for instance the neuroleptics and some 'sedative' antidepressants. As for anxiety and agitation in schizophrenia, it is well recognized to be poorly responsive to tranquilizers, agitation being well controlled by the neuroleptics, but anxiety less well (31). Unfortunately, it is not possible to state that neuroleptics should be restricted to the treatment of manifest psychoses and tranquilizers to that of non-psychotic patients with manifest anxiety. There are some clinical facts preventing such clearcut guidelines (31). First, some apparently non-psychotic patients may benefit from antipsychotic agents. Secondly, certain patients considered as suffering from a borderline psychosis related to schizophrenia, for instance with affective features, may respond reasonably well to antidepressants and not so well to neuroleptics. There is also the management of anxiety encountered in depression that can, in some cases, respond either to tranquilizers, to neuroleptics, or to 'sedative' antidepressants.

Placebo, various non-pharmacological factors (45, 46, 47), as well as various forms of psychotherapy or even simple reassurance, meditation, relaxation techniques can also relieve anxiety. Therefore, anxiolysis is not an exclusive pharmacological property, and can occur without drugs. These various factors make the clinical evaluation of the efficacy tranquilizers difficult from a methodological standpoint (1, 5, 23, 24, 30, 54). Moreover, neurotic symptoms respond differentially to tranquilizers (47). Indeed, *Rickels* pointed out that pure obsessive-compulsive, dissociated and phobic states, as well as conversion hysteria, either respond only mildly or fail to respond to these anxiolytic agents. In addition, he underlined that, in primarily anxious patients, some neurotic symptoms show a better response than others, and that, for instance, tranquilizers are considerably more effective in relieving symptoms of anxiety and somatization than in alleviating obsessive compulsive and interpersonal sensitivity complaints.

Anxiety is an emotion that can be independent from vigilance, from consciousness. Indeed, it may occur during sleep, accompanying dreams or nightmares and has early drawn psychonalytic interest (14, 15). It also can be experienced in various states of altered consciousness; pathological or induced by hypnosis. Clinically, the occurrence of sedation as expressed by a feeling of drowsiness or sleep, i.e., impairment of vigilance, is not desirable and constitutes

an annoying, troublesome side effect. All this emphasizes the fact that clinically the anxiolytic effect can be obtained without altering vigilance or consciousness; that the anxiolytic action is clearly different from the sedative and hypnotic ones.

From the literature, it therefore becomes apparent that clinically the sedative action can be defined as an unspecific calming action affecting the psychomotor sphere, and/or anxiety with its manifestations, and/or vigilance. A drug can abate psychomotor agitation or excitement, reducing or not reducing anxiety, producing or not producing drowsiness or somnolence. The anxiolytic action is thus more specific with anxiety as a target symptom and affect very little or not at all psychomotor activity and vigilance at normal dose range.

Several years ago, *Lehmann* (38) pointed out the three basic elements he considered essential for a good tranquilizer: safety, effectiveness and reliability. In man, the ideal tranquilizer should therefore have the following characteristics: selective action against anxiety; induction of serenity without indifference, i.e., allow a normal level of anxiety; no action of psychomotor activity or vigilance; no habituation or addiction; lack of toxicity; low dose for an optimum effect.

For most non-psychotic anxious patients, a combination of supportive psychotherapy and of psychopharmacotherapy constitutes the treatment of choice. The various drugs used as anxiolytics do not eradicate anxiety or its cause, but bring on a welcome relief. Indeed, they are not curative, but palliative.

Conclusion

From a clinical viewpoint, although it is not easy to establish a clear-cut distinction between sedative and anxiolytic action, such a difference, qualitative and quantitative, nevertheless exists. Sedation is a more global phenomenon than anxiolysis, which is a more specific one. Anxiolysis can be obtained without impairment of normal psychomotor activity and alteration of the level of vigilance. Both anxiolysis and sedation can be induced, to some extent, either by non-pharmacological factors, or by various types of psychotropic drugs whose primary pharmacological properties and clinical purposes are not aimed at this.

To avoid further confusion in terminology, although it means introducing yet another term, it might be useful to utilize the name 'anxioleptic' instead of 'tranquilizer' in the classification of *Delay and Deniker,* in contrast to 'neuroleptics' and 'hypnotics'. Anxioleptics would thus designate specifically the class of drugs whose primary clinical action is anxiolytic, preferably without inducing sedation, i.e., without notable effect on psychomotor activity and/or vigilance.

References

1 *Ban, T.A.:* Methodological problems in the clinical evaluation of anxiolytic drugs; in *Vinar, Votava, Bradley* Advances in neuro-psychopharmacology; pp. 211–224 (North-Holland Publishing Company, Amsterdam, and Avicenum, Czechoslovak Medical Press, Prague 1971).

2 *Binder, H.:* Uber die Angst. Schweiz. med. Wschr. *79:* 705–711 (1949).

3 *Boissier, J.R. et Simon, P.:* Psychopharmacologie expérimentale et prévision de l'activité des substances psychotropes; in *Freyhan, Petrilowitsch, Pichot,* Psychopharmacologie clinique. Probl. act. pharmacopsychiat.; vol. 1, pp. 100–117, (Karger, Basle 1968).

4 *Brenner, C.:* An elementary textbook of psychoanalysis (Anchor Press-Doubleday, New York 1974).

5 *Davies, B.:* Effects of anxiolytics in normal subjects; in *Vinar et al.* Advances in neuro-psychopharmacology; pp. 179–183 (North-Holland Publishing Company, Amsterdam and Avicenum, Czechoslovak Medical Press, Prague, 1971).

6 *Delay, J.:* Introduction à l'étude des neuroleptiques; in Journées Thérapeutiques de Paris; pp. 181–192 (Doin et Cie, Paris 1958).

7 *Delay, J.:* Intervention à propos de la terminologie et de la classification des médicaments psychiatriques. Symposium de Psychopharmacologie II Congrès International de Psychiatrie, Zurich 1967; in Psycho-Pharmacology Frontiers; pp. 167–172 (Little Brown, Boston 1959).

8 *Delay, J. et Deniker, P.:* Méthodes chimiothérapiques en psychiatrie. Les nouveaux médicaments psychotropes (Masson et Cie, Paris 1961).

9 *Deniker, P.:* Tranquillisants et neuroleptiques en pratique thérapeutique; in Journées Thérapeutiques de Paris, pp. 305–326 (Doin et Cie, Paris 1958).

10 *Deniker, P.:* Différences entre les médicaments neuroleptiques, tranquillisants et hypno-sédatifs: in *Brill, Cole, Deniker, Hippius, Bradley* Neuropsychopharmacology, pp. 87–89 (Excerpta Medica Foundation, Amsterdam 1967).

11 *Ellenberger, H.F.:* A clinical introduction to existential phenomenology and existential analysis; in *May, Angel, Ellenberger* Existence. A new dimension in psychiatry and psychology (Basic Books, New York 1958).

12 *Ey, H.:* Etudes psychiatriques. Aspects sémeiologiques, 2nd Ed. (Desclée de Brouwer et Cie, Paris 1950).

13 *Eysenck, H.J.:* Psychological aspects of anxiety; in *Lader* Studies of anxiety. Br. J. Psychiat. pp. 7–20 Special publication No. 3 (1969).

14 *Freud, S.:* A general introduction to psychoanalysis (Liveright, New York 1935).

15 *Freud, S.:* The interpretation of dreams; in *Brill* The basic writings of Sigmund Freud; pp. 179–549 (Random House, New York 1938).

16 *Fromm-Reichmann, F.:* Psychiatric aspects of anxiety; in *Thompson, Mazer, Witenberg.* An outline of psychoanalysis; pp. 113–133 (Random House, New York 1955).

17 *Ginestet, D.:* Différences entre neuroleptiques, tranquillisants et hypno-sédatifs dans leurs applications et leur efficacité pour le traitement des désordres psychiatriques: in *Brill, Cole, Deniker, Hippius, Bradley* Neuropsychopharmacology; pp. 138–145 (Excerpta Medica Foundation, Amsterdam, 1967).

18 *Giurgea, C.:* Pharmacological criteria for the classification of tranquilizers; in *Cerletti and Bové* The present status of psychotropic drugs; pp. 154–167 (Excerpta Medica Foundation, Amsterdam 1969).

19 *Greenblatt, D.J. and Shader, R.I.:* The clinical choice of sedative-hypnotics. Ann. intern. Med. *77:* 91–100, 1972.

20 *Greenblatt, D.J. and Shader, R.I.:* Drug therapy: benzodiazepines, part 1. New Engl. J. Med. *291:* 1011–1015 (1974a).
21 *Greenblatt, D.J. and Shader, R.I.:* Drug therapy: benzodiazepines, part 2. New Engl. J. Med. *291:* 1239–1243 (1974b).
22 *Harvey, S.C.:* Hypnotics and sedatives. The barbiturates; in *Goodman and Gilman* The pharmacological basis of therapeutics; 5th ed., pp. 102–123 (Macmillan, New York 1975).
23 *Hollister, L.E.:* Methodological considerations in evaluating antianxiety drugs. J.clin. Pharmac. *10:* 12–18 (1970).
24 *Hollister, L.E.:* Clinical use of psychotropic drugs (C.C. Thomas, Springfield 1973).
25 *Jaffe, J.H.:* Hypnotic and sedatives; in *Jarvik* Psychopharmacology in the practice of medicine; pp. 327–342 (Appleton-Century-Crofts, New York 1977).
26 *Kales, A. and Kales, J.D.:* Sleep disorders – recent findings in the diagnosis and treatment of disturbed sleep. New Engl. J. Med. *290:* 487–499 (1974).
27 *Kales, A.; Kales, J.D., and Bixler, E.D.:* Insomnia: An approach to management and treatment, Psychol. Ann. *4:* 28–44 (1974).
28 *Kales, J.D.; Bixler, E.P., and Scharf, M.D.:* Effectiveness of hypnotic drugs with prolonged use: flurazepam and pentobarbital, Clin. Pharmac. Ther. *18:* 356–363 (1975).
29 *Kielholz, P.:* Angst-psychische und somatische aspeckte (Huber, Berne, Stuttgart 1966).
30 *Kingstone, E.; Villeneuve, A., and Kossatz, I.:* Double-blind evaluation of prazepam, chlordiazepoxide and placebo in non-psychotic patients with anxiety and tension. Some methodological considerations. Curr. Ther. Res. *11:* 106–114 (1969).
31 *Klein, D.F.:* Treating anxiety; in *Hackett* Anxiety. Decision at the synapse; pp. 31–33 (Medcom, New York 1975).
32 *Klein, D.F. and Davis, J.M.:* Diagnosis and drug treatment of psychiatric disorders (Williams and Wilkins Company, Baltimore 1969).
33 *Knoll, J.:* Screening and grouping of psychopharmacologic agents; in *Sigler and Mayer* Animal and clinical pharmacologic techniques in drug evaluation; vol. 2, pp. 305–321. (Year Book Medical Publishers, Chicago 1967).
34 *Koch-Weser, J. and Greenblatt, D.J.:* The archaic barbiturate hypnotics. New Engl. J. Med. *291:* 790–791 (1974).
35 *Lader, M.:* The nature of anxiety. Br. J. Psychiat. *121:* 481–491 (1972).
36 *Lader, M. and Marks, I.:* Clinical anxiety (Heinemann Medical Books, London 1971).
37 *Lehmann, H.E.:* Differences in behavioural effects in humans; in *Brill, Cole, Dniker, Hippius, and Bradley* Neuropsychopharmacology, pp. 131–137 (Excerpta Medica Foundation, Amsterdam, 1967).
38 *Lehmann, H.E.:* Tranquilizers: clinical insufficiency and need; in *Cerletti and Bové* The present status of psychotropic drugs, pp. 168–175 (Excerpta Medica Foundation, Amsterdam 1969).
39 *Marks, I. and Lader, M.:* Anxiety states (anxiety neurosis): a review. J. nerv. ment. Dis. *156:* 3–18 (1973).
40 *May, R.:* Freud's evolving theories of anxiety; in *Thompson, Mazer and Witenberg* An outline of psychoanalysis; pp. 97–112 (Random House, New York 1955).
41 *Perkins, R. and Hinton, J.:* Sedative or tranquillizer? A comparison of the hypnotic effects of chlordiazepoxide and amylobarbitone sodium. Br. J. Psychiat. *124:* 435–439 (1974).
42 *Pöldinger, W.:* Compendium de psychopharmacothérapie, 3e ed. (Editions Roche, Bâle 1975).

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