F. letters

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Dear Dr. Dykes,

I have had an opportunity to review the chapter #30, "Antidepressants" and am pleased to share the following notes and comments. These follow the pagination of the text.

pg. 1: The classification of depression is that which has been used for many years. However, in the past decade, other classifications have been developed, and these are more directly useful in the determination of treatment. The terms: Bipolar, unipolar, and neurotic depression, with the subtypes of involutional, depression of the elderly, and post-partum seem to have more use in regard to drug selection. I urge you to review the classifications of Woodruff and Guze, Spitzer, and Robins to name some U.S. authors who have shown the merit of a revised classification.

This classification is particularly useful in allowing a place for the use of lithium in the management of depression as it may appear in bipolar disease. The omission of lithium may be a significant omission, despite the fact that the use of lithium in depression is still in research. This is particularly true since the report includes the use of stimulants and monoamine oxidase inhibitors-- two treatments that are clearly no longer considered efficacious except under exceptional circumstances.

pg 4: The statement that 'different patients given the same dose are caused by genetic. . ." seems strong to me. The finding of genetic components is a suggestion at best and 'are' could be changed to 'may be'.

The recommendation that therapy with the antidepressants should be started with low doses, combined with the later dosage recommendations in the individual sections on each compound is unfortunate for a number of reasons. For the most part, these compounds are effective only when given in 'adequate' dosages/ When one asks clinical psychiatrists who use antidepressants actively, dosages are

rarely started slowly, except in the elderly, and mean dosages for imipramine are 250-350 mg/day. The recommended dosages in the PDR are a bureaucratic balance arrived at in discourse by lawyers and administrators, which somehow is repeated in official reports. In checking the summaries for the use of imipramine by Klein & Davis, Hollister, Cole & Davis, and Fink & Abrams, the recommendations are for the higher dosages.

I believe that a major cause of failure in treatment with antidepressants is inadequate therapy, and unrealistic schedules.

In a similar vein, the suggestion that treatment should be given for 3 to 6 months and then reduced gradually is a plea for a regimen that is not common in my practice. Patients who do well, will not continue medication beyond the second month. If their symptoms persist, they will also not continue beyond the third month, particularly since they will request and obtain a change in prescription or a change in physician. If dosages are raised rapidly and effective levels obtained, a treatment response can be expected in 2-5 weeks; if sustained for 4-6 weeks thereafter, then therapy should be terminated and the patient seen more regularly in follow-up. As an example of a more vigorous approach to therapy, the recommendations from some European centers for the use of intravenous thymoleptics given by infusion over two to five days show some promise and their findings are consistent with the experiences cited above.

pg 5: The concurrent use of MAOI and thymoleptics may be recommended under certain conditions, notably in treatment failures to thymoleptics alone and ECT.

The last sentence regarding deanol is gratuitous. The sentence should read ' . . . as an antidepressant has not been demonstrated."

pg 6: The suggestion that other agents, as the antipsychotic agents, may be useful as adjuncts to therapy is partially correct. There is considerable evidence that antipsychotic agents (thioridazine, chlorpromazine) have been iused successfully in treating some depressive, not as adjuncts but as primary therapy. See refernces to work by Hollister and by myself and Klein in the early 1960's.

pg 7/8: It seems worthwhile to consoder the inclusion of some reference to the use of lithium; since this section is a grab-bag of assorted recommendations. With regard to the report of the unsuccessful use of TRH, this seems a bit harsh since the results are not yet in and the studies are still in progress. There seems some unusual selection of drugs included (deaner) and those rejected (TRH) when the evidence for deaner is non-existent, and that for TRH still under study. I would be more judicious in suggesting that TRH is the first of a series of peptides under study and that such investigations should be followed with interest.

pg 12: Fatalities are rare, and the tone of the paragraph is too strong

pg 14: Regarding the question of the concurrent use of guanethidine and thymoleptics, I have no experience.

pg 10: The combined use of thymoleptics and MAOI has been interdicted based largely on anecdotal and uncontrolled studies. As you suggest, lately some authors have suggested both regimens may be used concurrently. If true, then the caveat on this page is too strong and the paragraph may be rewritten indicating that some reports ahve been made but these are unsupported and that combined use may be given judiciously. (Considering the low rate of response of depressives to MAOI, I wonder why anyone would want to use the MAOI alone or in combination, except specialists who have adequate hospital facilities at their disposal. From a cost/benefit ratio analysis, the use of MAOI should be limited to occasional use by qualified specialists.

pg 19: Dosages of imipramine are from the PDR and are low. Single doses at night are useful; the reports beginning in 1961 show that the experience has been a lengthy one. See comments page 1.

page 29: A few years ago, I had an occasion to review the data for the recommendation of combined drug therapy. The dosages are low and the data unconvincing. Unless there is some recent data (since 1972) to justify the recommendation of a combination, I can recall no data, including those presented by the manufacturer, that would justify the recommendation even on a 'may be more useful' basis. The data for the successful use of the single drugs doxepin in cases wheree anxiety and depression co-exist is more convincing, and that conviction is a weak one.

To answer your specific questions: for MAOI, see comment on page 10; for single daily dosage, see below; and for guanethidine, see page 14.

It is reasonable to stress once daily dosage for the thymoleptics, particularly if this dosage is given at night, since the evidence of the efficacy is clear. For MAOI, there is no such evidence to my knowledge (see pg 10 above).

I trust these comments are helpful. I am less than enthusiastic about the chapter since the format follows our understanding of some years ago; and I do believe that some pregress has occurred, notably in dosages of thymoleptics; diagnoses; use of lithium; single administration; relation to ECT; and the downgrading of MAOI, stimulants which are reflected unclearly in the present document.

Thank you for the opportunity to raise some questions.

Sincerely yours,

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