

CONFERENCIA MAGISTRAL

THE CONCEPT OF MELANCHOLIA AND ANTIDEPRESSANT TREATMENT

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INTRODUCTION

Why have we on this occasion chosen this particular topic? At first glance it does not seem too interesting, as among psychiatrists, clinical psychopharmacologists and other highly ranked scientists who work with molecular biology, there appears to be a firm conviction that the introduction of DSM-III (1) in 1980 presented a major innovation in clinical psychiatry, which put an end to the insecurity and disagreement found before 1980 regarding the diagnostics and classifications of depressive disorders.

It is correct that the introduction of DSM-III was a paradigmatic change from nosological to syndromatical diagnostics and classifications. It is also correct that the previous classifications of depressive disorders were based on prototypical descriptions of the illness with unknown, but presumed aetiologies, with ill-defined boundaries and low reliability, which was suggested to impede the quality of research and of clinical psychiatry (2).

In this context, DSM-III introduced a purely descriptive non-aetiological classification with operationally defined categories based on diagnostic criteria with proven high reliability.

DSM-III became an immediate success - both in research settings and in clinical psychiatry. Its use spread all over the world in the decade following its introduction, with DSM-IV (3) and ICD-10 (4) taking over in 1994.

Little attention, however, was focussed on validity of the classification systems.

In other words, did this mean that these classification systems - for example in randomized clinical trials (RCT) with antidepressants - included the correct patients in the efficacy studies? Or was it still necessary to use both qualitative diagnostic rating scales as well as quantitative rating scales, the latter to be able to classify the severity of depression? Did we have to abandon the schooled aetiological and biological way of thinking, presented by Kraepelin in 1899, by his introduction of the concept of "endogenous depression"? (5).

The debate during the recent years shows that this is not the case. More and more data show us that tricyclic antidepressants compared with, for example, SSRIs have a significantly better effect in the treatment of severe depressions and recent studies question whether placebo controlled studies show that SSRIs are more effective than placebo (6-15).

Consequently, the credibility of the randomized controlled studies is challenged. But it is all clear that we cannot overlook the existence of subtypes of depression, such as endogenous depression or melancholia and moderate to severe depressions (16, 17), which are not specifically mentioned in most of the RCT-studies. The significance of these problems regarding treatment of depressive patients in the year 2003 is unknown (17).

Hence, in the following we have chosen to make a historical review with special focus on the concept of melancholia and antidepressant treatment, thereby trying to enlighten whether the present debate has roots all the way back to the past.

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THE DISCOVERY OF ANTIDEPRESSANTS (1950–1960)

This part is dedicated to the history of Roland Kuhn and Imipramine. Imipramine was synthesized in 1898 by Thiele and Holzinger, who described its chemical characteristics, but had no ideas for a possible use for it (18).

The centralizing structure, a three-ring or tricyclic structure, resembled the phenothiazines, which also had a three-ring central structure. As is well known, the phenothiazine, chlorpromazine, was discovered in the early 1950's and was accepted as an antipsychotic drug in 1952.

Although the discovery of imipramine came after the discovery of chlorpromazine, the discovery of the former was in many ways much more remarkable than that of the latter.

Chlorpromazine has clearly apparent effects, which have an onset within an hour. Imipramine, as will become clear, had none of these qualities. Like chlorpromazine, the development of imipramine came from, at that time, an interest in antihistamines. One of the antihistamines, promethazine, was used in anaesthesia and was reported to quicken the pace. These reports led Geigy to look further to this compound. As usual, the chemists were asked to make a series of derivatives, and a series of forty-two related components was put together. These were tested on animals for sedative and thermolytic properties. All of the series were antihistaminic and anticholinergic (6). Some were sedative and some were thermolytic and these few were selected to be tried on humans. Based on the animal and human tests, it was suggested that the series might be useful in anaesthesia, or might at least be hypnotic. The idea that there might be some other psychotropic action was not there, because at that time, in 1948, the antipsychotic effect of chlorpromazine had still not become apparent.

One compound was selected for clinical testing. This was G22150 (imipramine). As with the pattern of development of chlorpromazine, imipramine was given during 1950 to a wide range of clinicians to test it. This group included some psychiatrists among which was Roland Kuhn, at the Münsterlingen Hospital near Konstanz, Switzerland. Testing a drug at that time might involve little more than giving the drug on one or two occasions to a number of patients, often regardless of diagnosis. The result of the study was that no clinical effect was found. It did not even seem to be a useful sedative, a conclusion Kuhn agreed upon.

In 1953, at a time when the use of chlorpromazine had begun to spread in Europe, Kuhn claimed that he in 1950 might have seen some signs of effect similar to chlorpromazine (18).

Geigy then decided to set up a new study including 300 patients with schizophrenia and other conditions. The study design was that those on chlorpromazine were taken off that drug and put on imipramine, while those newly admitted patients, who were drug-free, also had imipramine. Many of the patients previously on chlorpromazine began to deteriorate. Some appeared to become hypomanic, and when one patient escaped from the hospital and rode into town on a bike in his nightshirt, singing at the top of his voice, Geigy decided to discontinue the study.

Kuhn and some of the other clinicians, however, claimed that they have seen antidepressant effect in depressed patients. Kuhn and others, including researchers from Geigy, spent time on several occasions trying to draw lessons from the events, and a final conclusion was drawn in 1955 suggesting the idea that imipramine might be an antidepressant. Geigy then suggested to Kuhn the idea that he might try out imipramine again in depressed subjects. A second study was set up to look at the effects of imipramine in depressed patients.

Forty patients were ultimately studied, but the responses of the first three depressed patients were so dramatic, that company scientists, ward nursing staff and Kuhn doubted that the treatment was effective and the study was stopped.

On September 1957 he presented his research at a poorly attended session of the Second World Congress of Psychiatry in Zurich. The presentation did not electrify many in the audience. The rest of the meeting remained unaware that they had missed something important (6).

In 1958 Kuhn had treated over 500 patients over a three-year period. He had picked out the features of a syndrome that he felt particularly likely to respond, a state Emil Kraepelin in 1899 had introduced as “endogenous depression” (melancholia) (5). Kuhn's patients typically were described as having the following symptoms (18):

- general retardation in thinking and acting
- their oppressive mood was worse in the morning, but improved in the afternoon
- loss of interest
- slept poorly
- had lost their appetite
- were preoccupied of hopelessness, guilt and despair.

As regards symptomatology, his description of depression was very close to Kraepelin's concept of endogenous depression found in “manic-depressive insanity” and very close to what is called major depressive disorders, melancholic features in DSM-IV or in ICD-10 depressive episode with somatic symptoms.

Kuhn described that treatment with imipramine produced an increase in vivacity and restoration of

interest in activities in general and social interaction in particular. Sleep was restored and appetite was stimulated. Although improvement might be apparent after two to three days, Kuhn claimed that it could take up to four weeks to become established.

He described all the side effects now associated with tricyclic antidepressant use. He also proposed a dose range that remains to-day. He argued that treatment with imipramine is symptomatic in the sense that, if stopped, while the underlying disease is active, it will lead to relapse of symptoms. Even as early as 1958, he claimed to have had patients in treatment with the drug for as long as two years with good results concerning maintenance efficacy.

In November 1957, imipramine was launched in Switzerland and in the spring of 1958 in a number of European countries under the brand name Tofranil[®].

In brief, the discovery of imipramine was made by a process of empathy. Without a deep, preverbal identification with the patients, Kuhn implies, the discovery would not have been made. He has contrasted the approach with the impersonal processes of modern research with its double-blind randomized methods and concern for quantifiable rating.

Kuhn discovered the response of a particular kind of depression – endogenous depression – to a particular form of drug treatment (6).

TRICYCLIC ANTIDEPRESSANTS AND THEIR THERAPEUTIC EFFICACY (1960-1970)

Amitriptyline was launched in 1961(19). It is interesting to read the history of amitriptyline especially in the light of how SSRIs were introduced in the 1980's (6). The Merck Company approached a number of USA investigators, including Frank Ayd, to look at amitriptyline, a drug almost chemically identical to imipramine. They too wanted to investigate for possible anti-schizophrenic properties, but during the study period Frank Ayd and his co-workers, possibly influenced by Kuhn, who visited USA at that time, asked the company for a trial with amitriptyline in depression. Ayd gave the drug to 130 depressed patients and in 1960 he reported the benefit of the drug in much the same kind of patients Kuhn had argued were helped by imipramine. However, the Merck Company was smarter than that. They approached Frank Ayd, who in 1961 had written the book "Recognizing the Depressed Patient" (20). In this book, Ayd argued that depression was not something which was found in asylums, but rather could be diagnosed in general medical wards and in primary care.

So, where Kuhn had argued that imipramine revealed

the shape of a particular disorder (endogenous depression), Merck was keen to reveal the shape of depression to as many physicians as possible, as quick as possible. Therefore in essence, Merck not only sold amitriptyline, it also sold an idea, and amitriptyline became the first antidepressants to sell at substantial amounts.

In a way, the discovery of amitriptyline finally led to the acceptance of imipramine, but Kuhn's discovery of the "response of a particular kind of depression – endogenous depression – to a particular form of drug treatment" was not accepted. During the 1960's it was instead clinically accepted that treatments with antidepressants were specific for "depressive illness". With the emergence of the tricyclic antidepressants, a premium was put on ideas congruent with the proposal that these were specific treatments for depressive illness.

In the 1960's a number of figures such as Sir Martin Roth, Max Hamilton and Hermann von Prag, came up with formulations that appeared to coincide with the action profile of tricyclics. Hamilton (21) produced a rating scale that became the gold standard for the assessment of antidepressant effects, which conceded to fit almost hand-in-glove with the profile of imipramine, so much so that there are to-day concerns that its use as a standard rating instrument may be inhibiting the development of new compounds that are unlike imipramine, for example SSRIs.

Sir Martin Roth and his colleagues from Newcastle formulated in the 1960's the issues surrounding vital or non-vital depressions. They came up with operational definitions to distinguish between endogenous and non-endogenous depressions (22). The implication was that endogenous depression was a biological disorder, probably stemming from constitutional or genetic factors, given that it supposedly arose out of the blue. Accordingly it was only appropriately treated pharmacologically or with ECT. Non-endogenous or reactive or neurotic depressions, in contrast, stemmed from adversity and could probably be managed psychotherapeutically on the whole. Clearly this formulation fitted very nicely with the amine theories of depression when they emerged in 1965 and with the fact that the tricyclics were amine reuptake inhibitors. In other words, endogenous depression appeared to be confirmed as a categorical disease and as an appropriate target for specific drug treatments.

The discussion, however, concerning their use, efficacy and effectiveness started by the Merck Company in 1961, continued the following years. The following general conclusions on the therapeutic efficacy were drawn (16):

- About 66% of all reports claim comparisons of TCA's and placebo indicates the effectiveness of drug treatment.

- No clear cut or consistent differences in clinical effects between the various TCA's have emerged.
- Although efforts to predict effectiveness on the basis of clinical data have led to conflicting results, a number of investigators have complained that TCA treatment in the so-called endogenously depressed patients is superior to other drug treatment.
- Even within diagnostically homogenous groups of depressed patients, including those endogenously depressed, the antidepressant effect was found to be variable.
- It was generally believed that in non-endogenously depressed patients, TCA's have no specific antidepressive effect apart from a sedative effect.

TRICYCLIC ANTIDEPRESSANTS PLASMA CONCENTRATION/THERAPEUTIC EFFECT RELATIONSHIP IN ENDOGENOUSLY DEPRESSED IN-PATIENTS (1970 →)

In the late 1960's attention was focussed on the relationship between dose and plasma concentration. It was found that there was considerable variability in plasma levels for patients on the same dose of tricyclics (1, 11, 25).

Therefore, one of the explanations for the variable antidepressant effect found with tricyclics, including the endogenously depressed, could be that the individual variation in response was related to the corresponding variation in the plasma concentration of the various tricyclics.

During the 1970's, clinical pharmacokinetic studies were carried out to assess whether clinical response in patients better correlated to drug plasma concentrations than to drug doses and whether a correlation was strong enough to be use in the care of individual patients.

Especially in Sweden and Denmark, we very carefully discussed the designs of these types of new studies, taking methodological problems such as clinical and pharmacokinetic problems into consideration.

In this studies, the Newcastle scales (22) were used in the definition of endogenous depression, and severity of depression and measurement of therapeutic effect were controlled by using quantitative rating scales, and only hospitalized patients were randomized to the studies (26).

In this setting, we in Scandinavia, produced very consistent results, a plasma concentration therapeutic effect relationship of 3 tricyclic antidepressants: nortriptyline, imipramine and amitriptyline (26).

It was found that response was significantly better for patients with plasma levels below 180 microgram/l than for patients with plasma concentrations above that level.

Other studies, including very heterogenous groups of depressed patients, were unable to demonstrate any relationship between plasma concentrations and therapeutic efficacy (29).

So, from these data it was suggested that only in endogenously depressed patients a plasma concentration-therapeutic effect relationship exists (23, 26).

THE DANISH UNIVERSITY ANTIDEPRESSANT GROUP (DUAG)-STUDIES: TRICYCLIC ANTIDEPRESSANT VS. SSRIS (1980 →)

As mentioned in the introduction, there has appear in recent years a belief among psychiatrists that tricyclic antidepressants are the most effective treatment for the severe subtype of major depressive disorders, and in fact the most striking response to tricyclics have been seen in severely depressed in-patients.

The belief was first supported by a study from the Danish University Antidepressant Group in 1986 (30). In this randomized controlled trials with depressed in-patients (most of the patients were severely depressed), we found a significant superior response to clomipramine in comparison with the SSRI, citalopram (figure 1).

In the next study published in 1990 (31), we found a similar significant superior response to clomipramine in comparison with the SSRI, paroxetine (figure 3).

By analysing the two studies in more detail it was shown that most of the patients included in the studies were suffering from the melancholic subtype of depression according to the Newcastle 1965 scale (32).

During the following years a long row of controlled randomized studies was published with the same conclusion "that the efficacy of tricyclics is not superior in comparison to SSRI's". But nearly all of these studies have been carried out in out-patients (17, 32).

As we see the ongoing debate, we feel that the time has come to focus on characterizations of the different subtypes of depressed patients participating in randomized clinical trials, with different forms for recruitment strategies and thereby also of the design used in the trials.

THE DUAG-STUDIES RE-EVALUATED

As one can speculate as to why tricyclics may be more effective than SSRI's, from our point of view we have to answer the following questions:

1. Is there an advantage to targeting more than one biogenic system?

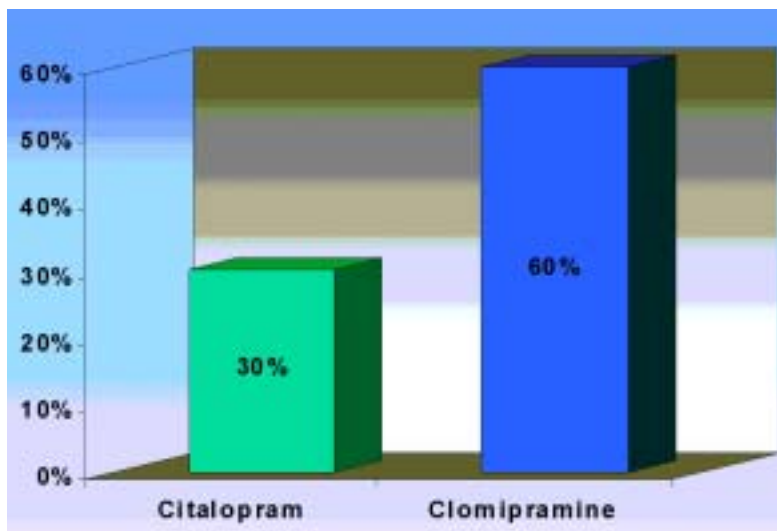


Fig. 1. DUAG-1. Citalopram vs. Clomipramine. Hospitalized patients (n = 102). % responders (HAM-D <8) after 5 weeks (p <0.005).

2. Could it be that depressed in-patients actually differ from out-patients?
3. It is only a function of severity of depression?
4. Is there an advantage to targeting more than one biogenic system?

In other words, are SSRI's too selective serotonin reuptake inhibitors, and do we need antidepressants with a broader pharmacological effect involving other biogenic amine systems, for example the noradrenaline system? This explanation is supported by the study with venlafaxine, a mixed serotonin and noradrenaline reuptake inhibitor (23).

This drug was found to be more effective than fluoxetine in severely depressed in-patients. Like TCA's

venlafaxine is selective for the noradrenaline and serotonin systems, but no study has been carried out comparing a TCA and venlafaxine in severely depressed or melancholic in-patients.

The hypothesis that hospitalized depressed patients have a different symptom profile from out-patients was tested by comparing 352 patients from three in-patients studies with 581 patients from three out-patients studies conducted in Denmark during the 1980–1992 period (32). All patients had major depression and were evaluated using the Hamilton Depression Scale (HAM-D) (33) and the Newcastle 1965 scale. In table 1 the items in which there was a statistical significant difference between in- and out-

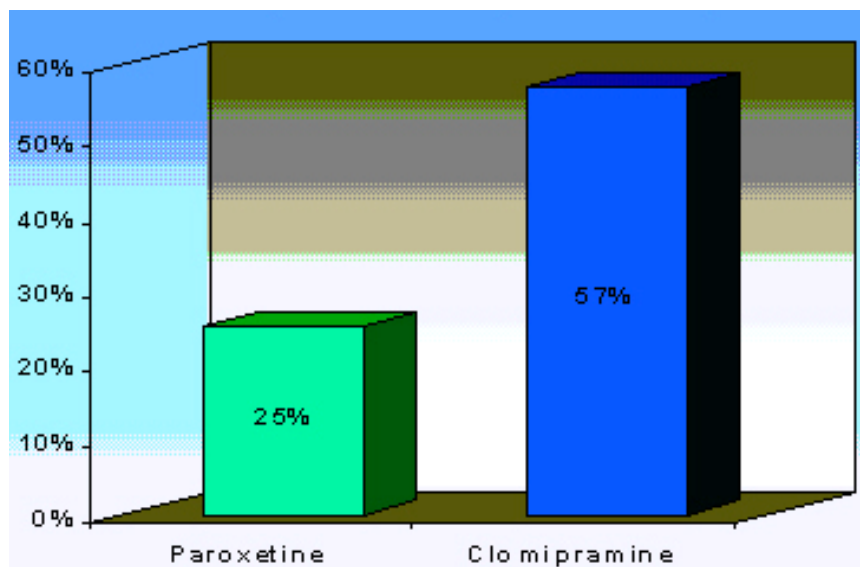


Fig. 2. DUAG-2. Paroxetine vs. Clomipramine. Hospitalized patients (n = 102). % responders (HAM-D <3) after 6 weeks (p <0.001).

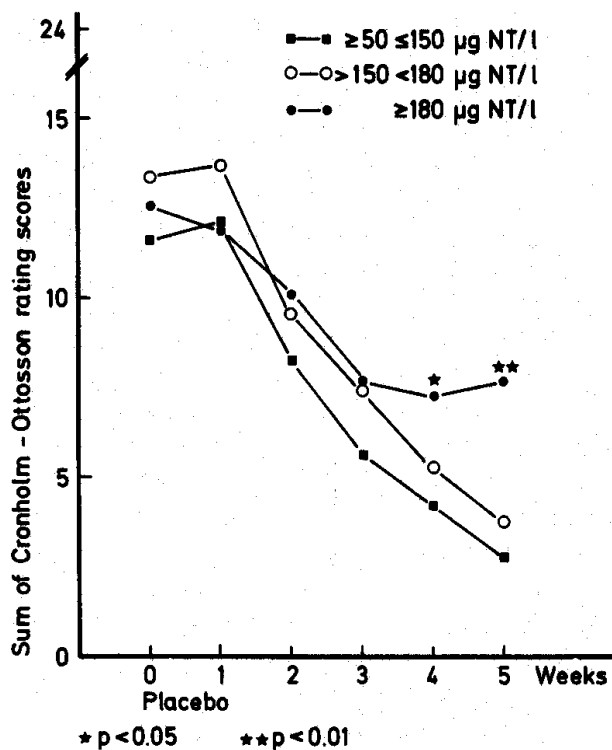


Fig.3. Nortriptyline plasma concentrationtherapeutic effect relationship in endogenously depressed in patients (n=54). Acta Psychiatr Scand 1973; 49:444-56; Psychopharmacologia 1976; 45:305-12.

patients is shown. It was found that most of the items in the in-patient groups showed a more melancholic type of depression (table 2). The Newcastle 1965 scale (34) classified 76% of the in-patients as melancholic depressed and in contrast only 40% of the out-patients were melancholic. The higher score in the Newcastle Scale was on the items “feelings of guilt”, “nihilistic delusions”, “distinct quality of depression”, “retardation” and “weight loss”. The lower score was on “psychological stressors” and “anxiety”.

CONCLUSION

From our data we conclude that the in-patients are characterized by symptoms signifying a more melancholic type of depression.

The pronounced difference in efficacy between clomipramine and the SSRIs in the DUAG studies may therefore be a consequence of the more frequent inclusion of melancholic symptomatology.

Is it only a function of severity of illness?

To answer the above question we have re-evaluated data from DUAG-1 and DUAG-2 and in this new retrospective study we have emphasized the effect goal on HAM-D (35), regarded as reduction between

TABLE 1. Differences in type of depressions in in- and out-patients according to The Newcastle 1965 Scale

| | In-patients | Out-patients |
|-----------------|-------------|--------------|
| Melancholia | 76% | 40% |
| Non-melancholia | 24% | 60% |

HAM-D total score at baseline and end-point of HAM-D total score in the relationship between severity of depression, choice of medication (clomipramine or SSRI), the presence or absence of melancholia.

The primary results indicate that the outcome of the treatment depends on the drug being used, the melancholic subtype (melancholia/non-melancholia) and the severity of depression at baseline (35).

A statistical significant correlation has been found between the effect goal (HAM-D reduction) and the variables: medication, melancholia/non-melancholia and severity of depression.

The difference in therapeutic efficacy between clomipramine and SSRI is largely marked in the group of depressive patients suffering from melancholia in severe depression.

PERSPECTIVES

Kuhn’s excellent work leaves us a central point repeated consistently over more than 40 years: “that imipramine treats a particular form of depression: Endogenous depression (melancholia)”. The result of our data implies the necessity to incorporate “melancholia” in future RCT-studies. It is necessary to undertake more prospective studies before a final conclusion can be drawn. At present there is no consensus regarding the definition of “melancholia” (17), but our data emphasize the importance of using the existing conceptions of melancholia (the DSM-IV and ICD-10 definitions) in the daily clinic.

TABLE 2. Differences in symptom profile according to HAM-D and the Newcastle 1965 scale between depressed out- and in-patients (n = 933; 581 respect 352)

| In-patients characteristics* | Out-patients characteristics* |
|--|-------------------------------|
| Depressed mood | Somatic complaints |
| Work and interest (reduced) | Hypochondriasis |
| Retardation | Psychological stressors |
| Distinct quality of depression | Anxiety |
| Weight loss | |
| Feelings of guilt | |
| Nihilistic delusions | |
| Suicidal impulses | |
| HAM-D total score (mean value 23 vs. 21) | |
| Age (median 51 vs. 46) | |

*Higher score p-value<0.0001 Stage KB et al. Acta Psychiatr Scand 1998; 98:432-36.

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