Interesting letters about course of affective disorders

from letters in Inter-psych <p>

compiled by Manote Lotrakul, MD.

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> Date: 22 Oct 95 12:34:50 EDT

> Is there any evidence in the literature that the use of antidepressants alters

> the course of depression in a negative manner? We do know that long term use of

> AD's prevents recurrence of depression but is it possible that exposure to AD's

> sensitizes the individual to more frequent future episodes once they have

> discontinued the medication?

>

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Reply

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There is, of course, the meta analysis by Suppes et al of Li

discontinuation studies that showed that after rapid discontinuation

of lithium bp patients were worse off than if they had never taken

the drug in the first place. I believe that a similar finding was

obtained in adolescents by Strober. I don't know of any formal

antidepressant discontinuation studies in unipolar depression that follow patients beyond one recurrence (i.e., the Ellen Frank/David Kupfer study). However, it has been my experience that some unipolar patients who discontinue effective antidepressants have a rebound of depression that is

1. worse than before and

2. now refractory to the previously effective treatment.

I would be happy to discuss reasons why this could occur if anyone is interested.

We might also want to discuss pts with rapidly recurrent unipolar depression and no evidence of bipolarity who develop more rapid recurrences of depression on antidepressants and fewer on lithium. This was mentioned years ago by Goodwin and I have seen it happen a few times myself.

Ask:

Nathan Munn wrote:

> I would very much like to hear why discontinuation of effective
> antidepressants may result in worse depressive episodes and subsequent
> development of refractoryness to the previously effective antidepressant.
> Frankly, this sounded a bit ominous.
>

Reply:

My own view of this (unproven of course), is that neuronal systems, like psychosocial systems, tend to maintain homeostasis. In the brain, this may result in compensatory increases in pathophysiology suppressed by antidepressants. For example, if an antidepressant tends to desensitize a given receptor, the neuron may try to make more receptors to compensate, or signals to the presynaptic neuron (through NO and other two-way avenues of communication) may lead it

to turn up its signal. Some of these compensatory mechanisms may involve changes in DNA transcription leading to more or less enduring alterations in ion channels, second messenger formation, etc.

When there are many drug molecules around, they may be able to override attempts of synapses to reset themselves back to their (customary) abnormal settings. But when the drug is withdrawn, there may be a big rebound of the pathological processes that results in a rebound of illness. When the drug is reintroduced, changes in receptors, second messengers and who knows what else may have altered responsiveness to the medication. This could also explain why pts sometimes get overwhelming side effects to a drug they tolerated easily during a previous episode.

Ask:

>

> Yes, I would very much be interested in any information about the potential

> for rebound with antidepressants.

Reply:

I discussed some of these points in my reply to Nathan Munn. I might add here that when the illness rebounds, it may do so in a new state that is no longer the same condition. The course may deteriorate, and new sx may appear. This could be related not only to rebound of pathological homeostasis, but also to the effect of the new episode of abnormal mood as a sensitizing stimulus that, via actions of neurotransmitters altered in response to stress of abnormal mood, alter gene transcription and therefore cellular function.

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> >>unipolar depression and no evidence of bipolarity who develop

> >>more rapid recurrences of depression on antidepressants and

> >>fewer on lithium. This was mentioned years ago by Goodwin and

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> >>Steve

> >>----------

> I too have seen this. I've also seen patients with ?unipolar depression where

> the EPISODE is worsened by AD's and ameliorated by Li.

> Goodwin and Jamison in their "Manic Depressive" Textbook emphasize the issue of

> cycling being as important a diagnostic consideration in determining manic-

> depressive disorder, as the issue of bipolarity i.e. a recurrent illness (even

> where there have been no manic episodes) is manic depressive.

>

> Raymond Behr, M.D.

This raises the interesting concept of a dimensional as well as a
categorical approach to dx. Within the broad range of pts with
unipolar major depression who never become manic, some have a lot of
recurrences, some a few; some have brief episodes, some prolonged
episodes; some are psychotic, some aren't; some have a lot of family
loading, some don't, etc. It seems to me that when lithium prevents
highly recurrent unipolar depression (as in brief recurrent
depression), or even when it prevents recurrences of cluster
headaches, it is acting as an anti-recurrence drug, not an antimanic
drug. There is some dimensional overlap between bipolar and unipolar
pts with highly recurrent depression, family loading, psychosis, and
maybe some other things, and possibly some treatment overlap as well.
Steve
Who really knows why. There is a nice review article of this topic in this
month's "green journal", (Am. J. Psychiatry) It is written by Post, et.al.
One other thing to keep in mind is that this does not happen to everyone

who has been on antidepressants. It is a relatively "new" finding.

Dale R. Grothe, Pharm.D.

Clinical Psychopharmacology Research Pharmacist

National Institutes of Health

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antidepressants may result in worse depressive episodes and subsequent

development of refractoryness to the previously effective antidepressant.

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Thank you in advance, Dr Dubovsky, for sharing your thoughts on this.

Nathan Munn

Helena, Montana, USA

Joe Schwab wrote:

>

> A couple of thoughts, I have listened to Kupfer/Frank discuss

> discontinuation of ADs & reoccurance of depression. Their remarks (as

> I recall) differentiated a 1 month taper from a 3 month taper. The 3

> month group faired much better in terms of the time to next depressive

> episode.

>

> The second thought comes from Bob Post (NIMH) & his discussions on

> cyclicity of disease paradigm (bipolar). This supports the notion that

> one needs to be aggressive in capturing control of the episode, and

> maintaining control (with chronic therapy). His remarks suggest that

> if the patient discontinues medication, they are more difficult to

> recapture. This cycling involves increasingly aggressive phsychopharm

> measures to recapture the patient, and a shorter time frame to next

> episode of depression (kindling).

>

> Joe

>

These are important points. We have to be aware that a lot of the
data we have are from studies of pts with no or just a few
recurrences and no chronicity. The more recurrent and chronic the
mood disorder, the more it tends to bounce back when rx is withdrawn.
I agree that faster taper produces more problems than slower, but
sometimes even dosage reduction (as in the first Frank/kupfer study)
leads to recurrence. The corrolary you mention is that early
aggressive rx is better, and that successful treatments probably
should be continued indefinitely in difficult to treat pts.
Steve
Is there really evidence that this happens? I know Post's kindling
theory, but thought it was pure speculation (re: bipolar disorder at
least), and not held up by other studies (mine included) showing that
"rapid-cycling" bipolar does not breed true in individuals or in
families. Also, I don't see this in the October green journal --
please give the complete citaiton.
> Reply to: RE>>Course of affective disorders

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> month's "green journal", (Am. J. Psychiatry) It is written by Post, et.al.
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> Dale R. Grothe, Pharm.D.
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> Nathan Munn

> Helena, Montana, USA

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> For a nice review of this issue of antidepressant-influenced changes in the

> course of affective illness, refer to the October issue of the "green

> journal" (Am. J. of Psychiatry) It contains a leading article written by

> Post, et.al. on this subject.

> Dale R. Grothe, Pharm.D.

>

What is the consensus of list members about whether antidepressants

do or don't worsen bipolar illness, and if so, how frequently do you

think this occurs and under what conditions?

Steve

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> depressive disorder, as the issue of bipolarity i.e. a recurrent illness (even

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>

It's an interesting differential between antidepressants causing cycling into a more severe depressive episode, vs antidepressants causing a transient increase in severity of unipolar depression. I have seen the latter from time to time, and it seems to be a predictor of an eventual good response to that or another antidepressant. Perhaps there is an initial increase in adrenergic responsiveness that causes increased distress and calls forth more pronounced down-regulation of the same system, with a therapeutic effect.

STeve