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Eight Discussion Starters on Aspects of Anxiety and Depression

Kevin Brewer

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Orsett Psychological Services
PO Box 179
Grays
Essex
RM16 3EW
UK

orsettpsychologicalservices@phonecoop.coop

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Kevin Brewer BSocSc, MSc

An independent academic psychologist, based in England, who has written extensively on different areas of psychology with an emphasis on the critical stance towards traditional ideas.

A complete listing of his writings at http://kmbpsychology.jottit.com and http://psychologywritings.synthasite.com/.

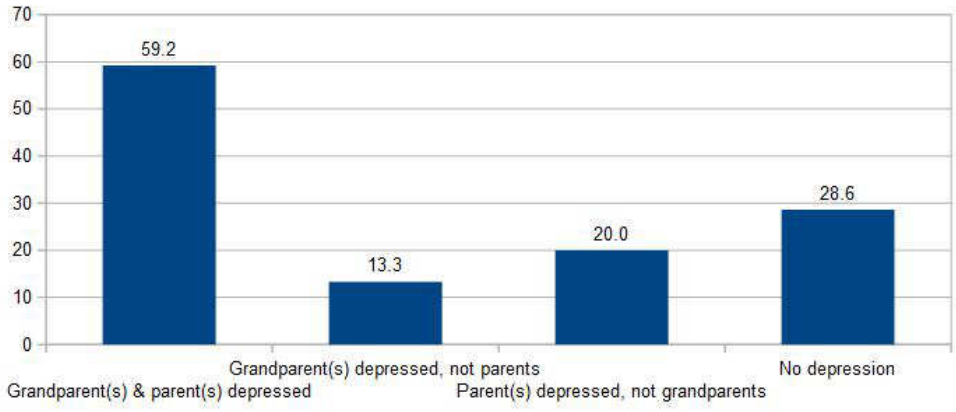
CONTENTS

1. RISK OF DEPRESSION

Family studies show an individual has two to three times the risk of depression if they have a first-degree relative (eg: parent) who suffered from it than not (Weissman et al 2005). These studies tend to concentrate on two generations (parent and offspring), while Weissman et al (2005) reported their twenty-year study that involved three generations.

The study began in 1982 with individuals with major depressive disorder (MDD) at outpatient psychiatric clinics in the north-east USA (generation 1; baseline). Further measures were taken after two, ten and twenty years, including from the offspring of generation 1 (called generation 2), and latterly their offspring (generation 3). A non-depressed control group were also recruited from the local communities in 1982. In 2002, there were 47 grandparents (generation 1), 86 offspring (generation 2), and 161 grandchildren (generation 3) (who were aged 8-15 years approximately).

Grandchildren of depressed generation 1 were more likely to suffer from a psychiatric disorder than grandchildren of the controls, though these differences were not statistically significant except for anxiety disorders (even after controlling for age and sex). The generation 3 individuals with a depressed generation 1 and 2 relative had the highest risk of any mental disorder (figure 1). When distinguishing only MDD sufferers in generations 1 and 2, the effect was stronger (figure 2).

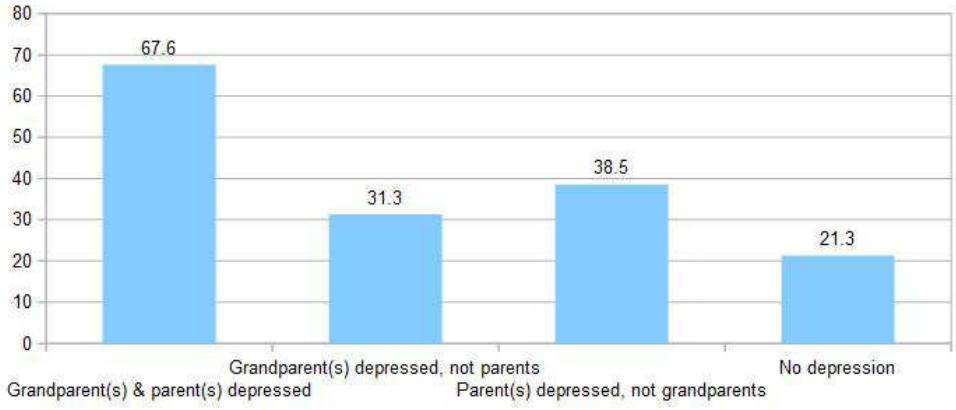


(Data from Weissman et al 2005 table 1 p32)

Figure 1 - Percentage of generation 3 who suffered from a mental disorder based on depression in parent(s) and grandparent(s).

Overall, the impact of having a depressed parent(s)

was greatest, irrelevant of the grandparent(s)' depression status, and anxiety was the most common disorder among generation 3 individuals. Weissman et al (2005) wondered if anxiety, particularly in the younger grandchildren (ie: pre-puberty) would be a precursor to later depression.



(Data from Weissman et al 2005 table 2 p33)

Figure 2 - Percentage of generation 3 who suffered from a mental disorder based on MDD in parent(s) and grandparent(s).

This study was not able to say that the generation 3 mental disorders were entirely genetic because environmental risks were present (eg: depressed mother and poor care of baby). Weissman et al (2005) concluded: "Because parents may provide both high-risk genes and a high-risk rearing environment, disentangling psychosocial and biological factors mediating the transmission of risk across generations is a challenge" (p35).

Questions

1. General - How useful are the findings when environmental risks still play an important part?

2. Methodology - What are two methodological weaknesses of the study?

3. Ethical - Would it be a good thing to tell potential parents that their offspring have a risk of depression?

4. Further research - What are the actual genes involve in the inheritance of depression?

2. WOMEN AND DEPRESSION

Women are more likely than men to be diagnosed with depression. There are a number of possible explanations for this observation explored by Cochrane (1995), but he preferred the last.

i) An artefact - ie: more women seek help than men and are thus counted. But self-reported general surveys still find the difference.

ii) Biological factors - The symptoms themselves may also vary: for women sadness is dominant compared to irritability, anger and recklessness with men. The hormonal changes in puberty may be relevant. Girls experience surges in oestrogen levels which increase susceptibility to cortisol (related to stress), while surges of testosterone in boys may protect against depression (according to studies with mice) (Westly 2010).

But no overall biological mechanism identified (Cochrane 1995).

iii) Long-term effects of child abuse - The argument is that more girls suffer abuse than boys, and this manifests as adult depression. But abuse does not lead to depression for all.

iv) Gender role socialisation produces increased female vulnerability - But women also experience this socialisation and do not suffer from depression.

v) Depression as a coping strategy for women - Cochrane (1995) argued for this explanation as men and women cope with distress in different "socially acceptable" ways.

PREGNANCY

The prevalence of major depression during pregnancy is around one in eight women (Leiknes et al 2015). Such women face an extra problem with treatment - namely, the effects of medication on the foetus (known as teratogenicity). Consequently, electro-convulsive therapy (ECT) is a possibility. But is it safe?

The American Psychiatric Association in 2001 stated that ECT has a "low risk and high efficacy in the management of specific disorders in all three trimesters of pregnancy" (quoted in Leiknes et al 2015). Leiknes et al (2015) were not convinced, and this prompted their literature review. The case reports of 169 ECT-treated pregnant women were found. Most received ECT during the

second trimester. Adverse effects (eg: foetal heart rate reduction; uterine contractions) were reported in 29% of cases. This led the authors to recommend ECT during pregnancy "only as last resort treatment under very stringent diagnostic and clinical indications" (p1).

Questions

1. General - Are there real gender differences in depression generally, or at different times in life?

2. Methodology - What are two methodological issues faced by studies of gender differences in depression?

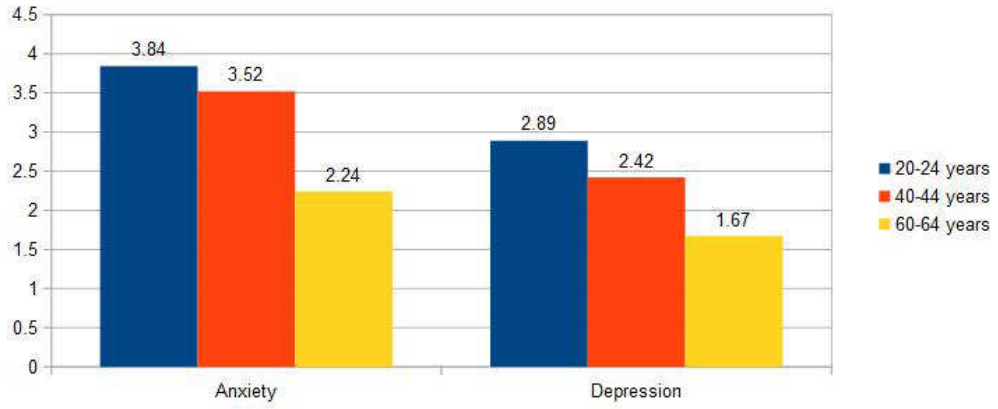
3. Ethical - If women are really more prone to depression, what are the implications of this for society?

4. Further research - Cochrane was writing in the mid-1990s, what has research subsequently found on the subject?

3. AGE DIFFERENCES

Approximately 1-6% of adolescents suffer from depression worldwide each year, of which about a half will have a recurrence within five years, and depression increases the risk of suicide 10-25-fold (Thapar et al 2010).

The reported symptoms of anxiety and depression vary with age. For instance, the PATH Through Life Project" found a decline (Jorm et al 2005). This involved groups of 20-24 year-olds, 40-44 year-olds, and 60-64 year-olds in Canberra, Australia, who completed the Goldberg depression and anxiety scales (Goldberg et al 1988) for the past month. There are nine items scored as yes or no for depression (eg: "have you felt hopeless?") and nine items for anxiety (eg: "have you been worrying about your health?". Younger respondents had higher scores than older ones (figure 3).



(Data from Jorm et al 2005 table 1 p1259)

Figure 3 - Mean anxiety and depression scores (out of 9).

Blazer and Hybels (2005) reviewed the risk and protective factors (table 1) for depression in later life and concluded that: "Older adults appear to be at greater risk for major depression from some biological causes... yet the frequency of major depression is lower... [and]... there is reason to believe that older adults who are cognitively intact and who do not suffer from significant functional impairment may be protected psychologically... and perhaps protected from some social risk factors compared to younger adults" (p1249).

- General biological risks - eg: hereditary; being female; medical illness.
- General psychological risks - eg: learned helplessness; neuroticism; external locus of control.
- General social factors - eg: stressful life events; bereavement; socio-economic disadvantage.
- Specific biological risks for older adults - eg: low levels of DHEA (dehydroepiandrosterone); Alzheimer's disease; stroke.
- Psychological protective factors - socio-emotional selectivity [1]; wisdom.

(Based on Blazer and Hybels 2005 table 1 p1242)

Table 1 - Risk factors and protectors for depression in later life.

Questions

1. General - Is depression a greater risk for a particular age group?

2. Methodology - What are the methodological problems with cross-sectional studies that simply compare different age groups at one point in time?

3. Ethical - What are the implications for allocation of resources if one age group is more prone to depression?

4. Further research - What have studies since Blazer and Hybels (2005) found on the subject?

[1] This suggests that the perception of limited time left to live leads older adults to focus on the positive rather than negative experiences.

4. MELANCHOLIA

Melancholia has a long history. For example, Hippocrates in the 5th century BC referred to it as due to "an excess of black bile whose fumes rose to the brain and made thoughts black" (Parker and Paterson 2014). But does it have a distinct place in the modern world of categories of mental disorder?

DSM-5 describes symptoms like anhedonia, early morning waking, and excessive or inappropriate guilt, which are common to both depression and melancholia, while ICD-10 does not use the term melancholia but has a category of "somatic symptoms" (Parker and Paterson 2014). Specific symptom-based measures have been developed like the Bech-Rafaelson Melancholia Scale (Bech and Rafaelson 1980), Newcastle Index (Carney et al 1965) [2], or the Sydney Melancholia Prototype Index (SMPI) (Parker et al 2013). The latter distinguishes twelve "descriptors" of melancholic and non-melancholic depression with "descriptors comprising both symptoms and illness correlates" (Parker and Paterson 2014).

The designers of the SMPI argued elsewhere (Parker et al 2010) that "'melancholia' may be 'mapped' more precisely by proceeding beyond reliance on symptoms only, and referenced how navigational global positioning systems work to the principle of 'triangulation' (ie: relying on a minimum of three satellites). Currently, diagnostic approaches employ either one reference point (symptoms) or two (symptoms and illness-associated factors). A third reference point – and one long pursued – is identifying causal factors, biomarkers or laboratory tests" (Parker and Paterson 2014 p3).

Looking for differences between melancholic and non-melancholic depression, life events as the cause would be less important for melancholic/endogenous or "clinical" depression (eg: Wakefield 2012). Brown et al (1994) found that life events were less important for the second, but not first, episode of depression.

Parker and Paterson (2014) noted the search for distinct biological markers of melancholia, including higher cortisol levels upon waking and less change during the day [3], an inflamed immune system, neurochemical imbalances, or differences in brain structure. Cognitive impairments (eg: numerical working memory) have also been reported.

Another way to distinguish melancholic depression is through the differential response to treatment. For example, less spontaneous remission in placebo groups, or a different response rate to various anti-depressants.

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[2] This distinguishes "endogenous" (melancholic) depression from "neurotic" (non-melancholic) depression.

[3] Taken as evidence of hyperactive hypothalamic-pituitary-adrenal axis functioning.

Though the studies can be contradictory (Parker and Paterson 2014).

Parker and Paterson (2014) admitted, in conclusion, that a "definitive indicator of melancholia remains to be identified" (p5).

5. DIET AND WEIGHT

The gut microbiome is "the community of bacteria and their genetic material living in the gut" (Dash et al 2015), and it may be the link between diet and depression, or more technically, between habitual dietary intake and the prevalence of or risk for depressive illness (Dash et al 2015).

For example, Lai et al's (2014) meta-analysis found that a healthy diet reduced the likelihood of depression by about one-fifth (as compared to a poor diet), while the Mediterranean-style diet reduced the risk by about one-third (Psaltopoulou et al 2013).

The nature of the "gut-brain axis" is being studied, but manipulation of the gut microbiota with probiotics, say, can produce depression-like behaviours. Gut microbiota has been found to influence the neurotransmitter serotonin (and its precursor trytophan) which may be the pathway of effect (Dash et al 2015).

The gut microbiota can also be altered by prenatal and early life stress. Offspring of stressed pregnant monkeys have differences in microflora concentrations compared to non-stressed mothers' offspring, for instance (Dash et al 2015).

Kivimaki et al (2009) found a bidirectional relationship between obesity, and depression and/or anxiety (common mental disorders) - ie: obesity increased risk of anxiety and/or depression, and anxiety and/or depression increased the risk of obesity. Previous studies had found the latter (Atlantis et al 2009).

Kivimaki et al (2009) used data from the Whitehall II study which follows a cohort of over 10 000 civil servants in London since 1985-88. The individuals were 35-55 years old at baseline, and the seventh follow-up point (which was used here) took place in 2003-4 (n = 4363 [4]). Self-reported questionnaires, and health check-ups occurred at each follow-up point.

In terms of the bidirectional relationship:

1. Anxiety and/or depression as risk for subsequent obesity - Individuals were divided into four groups for common mental disorders (ie: no symptoms, 1, 2 or 3 symptoms self-reported). Using the no-symptoms group as the comparison, the three-symptom group was twice as likely to be obese at a future follow-up point.

What are the possible explanations for anxiety and/or depression as a risk for obesity? Kavimaki et al (2009) offered the following:

[4] 72% were male, and those in the study still were significantly healthier than those who dropped out (Atlantis et al 2009).

- Anxiety and/or depression leads to over-eating and/or "comfort eating" of fatty/sugar-rich foods.
- Anxiety and/or depression leads to physical inactivity.
- Weight gain side-effects of anti-depressants.
- Dysregulation of the hypothalamic-pituitary-adrenocortical axis.

2. Obesity as risk for future anxiety and/or depression - Participants were divided into four groups for analysis based on number of follow-up points classed as obese (0, 1, 2 or 3). The three-occasions group were about one and a half times more likely to self-report common mental disorders at a later follow-up point than the 0 group.

Atlantis et al (2009) offered the following mechanisms for obesity leading to depression and/or anxiety:

- Obesity leads to actual or perceived stigma and discrimination, and in turn to depression/anxiety.
- Obesity is associated with socio-economic disadvantage and low physical activity, both of which are linked to depression.
- Obstructive sleep apnoea is common in obesity, and this is linked to depression.
- Dysfunction in hypothalamic-pituitary-adrenal axis.

Kivimaki et al (2009) admitted that they could not "provide complete of causality".

6. COGNITIVE BIAS MODIFICATION

Cognitive bias modification (CBM) is the "direct manipulation of a target cognitive bias, by extended exposure to task contingencies that favour predetermined patterns of processing selectivity" (MacLeod and Matthews 2012 quoted in Cristea et al 2015). There tends to be two types - attention bias modification (ABM) and interpretation bias modification (CBM-I). The former involves teaching individuals to avoid negative or threatening stimuli by focusing on neutral or positive stimuli. With CBM-I individuals are taught to interpret ambiguous stimuli in a positive rather than negative way (Cristea et al 2015) [5].

CBM assumes that "automatic" (or habitual) responses underlie anxiety and depression [6]. For example, individuals with social anxiety disorder automatically attend to their blushing, say, in social interactions and signs of boredom in others. This leads to negative self-evaluation, and increased anxiety. By associating a stimulus with a positive response, it believed that a negative response can be modified. For instance, pictures of a phobic object linked to positive images repeatedly. it is hoped that the cognitive modification will occur outside of conscious thought (ie: new habitual response).

Attention bias is measured with the dot-probe task commonly. Individuals are asked to respond as quicker as possible when a particular stimulus (probe) is shown on a computer screen. This probe is shown in the midst of different stimuli (eg: images presented for 500 ms). An anxious individual responds quicker to the probe if it follows a threatening image than a neutral or positive one, while depressed individuals can be slower to respond to the probe after a mood-congruent stimuli (eg: sad) (Hallion and Ruscio 2011).

CBM uses the dot probe task in this way. Two images are presented simultaneously - a threatening one and a positive one - and the probe appears afterwards in place of the positive one. "Over the course of many trials, participants are expected to implicitly learn the association between the benign stimulus and the target response and to begin attending selectively to benign stimuli" (Hallion and Ruscio 2011 p941).

In the case of an ambiguous sentence like "the man had convictions", anxious individuals are more likely to make a threatening interpretation of "convictions" (ie: criminal record) as opposed to strong beliefs. While

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[5] There is also concreteness training, and alcohol approach and avoidance training (Cristea et al 2015).

[6] More technically, Hallion and Ruscio (2011) stated: "a tendency to preferentially process negatively valenced information" plays a part in anxiety and depression (appendix 1).

depressed individuals have been found to interpret ambiguous sounds negatively (eg: die vs dye) (Hallion and Ruscio 2011).

In terms of therapy, with interpretation bias, individuals are presented with ambiguous sentences to complete - eg: "people think you are...", but with an answer fragment (eg: "fr_e_dly"). This is repeated to build up the positive interpretation bias (Hallion and Ruscio 2011).

Does CBM help reduce anxiety and/or depression? There are three older meta-analyses that have attempted to answer this question:

1. Hakamata et al (2010) - (12 studies included). ABM was significantly better in reducing anxiety than a control group.

2. Hallion and Ruscio (2011) - (45 studies included). CBM had a small effect on anxiety and depression together.

3. Beard et al (2012) - (37 studies included). Non-significant effects on subjective experience with ABM.

Cristea et al (2015) questioned the methodology of these meta-analyses:

a) It is not clear if only randomised controlled trials (RCTs) were included.

b) The quality of the RCTs were not considered.

c) Consideration of only a limited number of moderators of the effects of CBM.

d) Risk of publication bias.

In their recent meta-analysis, Cristea et al (2015) took these methodological issues into account as well as studies published since the above meta-analyses. The researchers performed a literature search up to May 2013, and included studies that met seven criteria (eg: participants randomised; comparison with control or another treatment). The methodological quality of the studies was rated on five criteria for RCTs (proposed by Cochrane Collaboration). There were forty-four published studies of forty-nine RCTs left after this process [7].

The studies varied in a number of ways, including:

i) Number of sessions of CBM (from 1-15).

[7] An initial search produced 738 records.

ii) Recruitment of participants (eg: students, patients).

iii) Location of CBM intervention (eg: laboratory).

iv) Compensation for participation or not (eg: course credit for students).

v) Type of CBM.

Only five studies met all five criteria for RCTs, and the majority (33/49) met three or less.

In comparison to a control condition, the overall effect of CBM for anxiety or depression was significant, but small. A sub-group analysis of clinical samples only found less of an effect (ie: non-significant). But the size of the overall effect was reduced by variation between the studies (heterogeneity), including outliers, and publication bias.

Cristea et al (2015) found a greater effect if participants were compensated for taking part in the study, and if the location of the intervention was the laboratory. Interestingly, the effect of CBM declined with the number of sessions (ie: negative correlation), while some placebo groups (ie: receiving "sham CBM") showed improvements. "Put together, these results seem to indicate that it is not unlikely that many positive CBM findings may have been influenced by a variant of the 'experimenter effect' or other experimental artefacts, unrelated to the scope and purported mechanisms of action of these interventions" (Cristea et al 2015 p14).

Any new treatment faces the "time lag bias" - "the phenomenon in which studies with positive results get to be published first and dominate the field, until the negative, but equally important, studies are published" (Cristea et al 2015). Thus, Cristea et al (2015) reported that effect sizes were significantly higher for older studies. Earlier studies of a treatment tend to be smaller, for example. There is also publication bias, where only studies finding significant effects are published. For example, if ten studies are published for this reason, is this ten out of a total of ten studies or ten out of one hundred studies (ie: ninety unpublished non-significant studies)?

Cristea et al (2015) felt that CBM received early interest as well because of "highly laudatory narrative reviews, comments and editorials, published before the efficiency of the new interventions had been established in well-powered, methodologically appropriate RCTs... Moreover, overtly positive pieces about CBM have been almost exclusively published in top-tier journals, thus contributing to indirectly enforcing the notion that we were witnessing the development of a powerful new therapy – 'a new clinical weapon' (MacLeod and Holmes

2012)" (Cristea et al 2015 p14).

Cristea et al (2015) stated in conclusion: "Given that CBM interventions are primarily intended as cost-effective therapeutic alternatives, alleged to have an impact on clinically relevant symptoms, we believe our results cast serious doubts on the majority of them having strong clinical utility" (p13). Other forms of therapy for depression, for example, they argued, have a greater benefit (eg: cognitive-behavioural therapy; CBT [8]).

APPENDIX 1 - COGNITIVE BIAS

Harkness et al (2005) found that mildly depressed students were more able to detect other people's emotions better than non-depressed individuals. Female students in Canada classed as depressed (n = 16) or not (n = 27) were asked to identify the emotions in 36 black and white pictures of eyes [9] [10]. The depressed students were correct on 78% of pictures compared to 69% for the non-depressed group. This is a significant difference.

Understanding other people's feelings has two stages - the ability to detect the emotion, and interpretation of that emotion. Harkness et al (2005) felt that depressed individuals are better at the first stage, but tend to make a negative interpretation in the second.

[8] Derek Draper (2006), a psychotherapist and former New Labour advisor, argued for CBT for anxiety and depression to be more available as a NHS treatment in the UK. It is low cost, scientifically proven, transforms lives, increases productivity, reduces anti-social behaviour, and makes people happy, he said.

[9] Four words were offered with each photograph, including positive (eg: friendly, confident), negative (eg: worried, hostile), and neutral (eg: preoccupied) ones.

[10] There were two control tasks, on which the two groups did not vary in accuracy - name an animal from a picture, and stating the gender of the eyes in the human photographs.

7. ANTI-DEPRESSANTS

The effectiveness of any treatment is affected by the adherence to its regimen [11]. For example, up to half of individuals with depression have discontinued their anti-depressants within six months (Hung 2014) [12]. The question is what factors or variables are linked to adherence, persistence, completion, or discontinuation of anti-depressants [13].

The factors can be grouped together (Hung 2014):

1. Socio-demographic factors

a) Age - older individuals have lower rates of discontinuation and longer time to discontinuation after starting the anti-depressants.

b) Ethnicity - In US studies African-Americans, minority ethnic groups, and immigrants have poorer adherence than Whites.

c) Gender - no consistent pattern.

d) Income level - poverty associated with lower adherence.

2. Clinical features of depression

a) Severity - some studies find that greater severity predicts non-adherence.

b) Type - eg: chronic (long-term) depression and longer time to discontinuation.

c) Co-morbid mental illness - depends on the co-morbid condition; eg: depression and anxiety greater adherence than depression alone, but less adherence when depression co-morbid with other psychiatric disorder.

d) Co-morbid physical illness - greater risk of drug interactions and discontinuation.

e) Pregnancy - pregnant women more likely to discontinue than non-pregnant ones.

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[11] The effectiveness of a treatment is established with randomised clinical trials (appendix 2).

[12] One explanation for a low response to anti-depressants is "covert heterogeneity" (appendix 3).

[13] Priebe et al (2013) reported that financial incentives were effective in adherence to anti-psychotics for patients with psychotic disorders. Seventy-five patients living in the community in England and Wales were offered £15 for each weekly or monthly injection over twelve months. Adherence in this group increased from 69% at baseline to 85% at one year compared to 67% and 71% respectively for the control group (n = 56).

3. Pharmacological factors

a) Side effects - these consistently predict discontinuation.

b) Treatment response - (ie: not helping depression): "common reason for non-adherence" (Hung 2014).

c) Type of anti-depressant - some difference between the types and "brands", but Hung (2014) gives a word of warning: "differences in adherence among anti-depressants might be due to bias from the study design, selling channel, sponsorship, types of insurance, different sub-types of depression or co-morbidities, and other factors" (p346).

d) Dosage - beginning with a sub-optimal dose "might provide patients with more time to become tolerant to the side effects of anti-depressants, [but] a sub-optimal dose might also lead to a poor treatment response, which is related to increasing non-adherence and discontinuation of anti-depressants" (p347).

Sanglier et al (2012), for example, compared switching anti-depressants or combining them with an increasing dosage of escitalopram. The non-persistence rates were 56%, 91%, and 39% respectively. But Hung 92014) is again cautious: "bias might result from the fact that the clinical characteristics of the patients in the three groups were different, because physicians might decide to use one of the three approaches based on a patient's clinical features" (p347).

4. Beliefs and attitudes of patients - beliefs and attitudes about depression and anti-depressants predict adherence. For example, the perception of anti-depressants as a necessity (eg: "my health depends on anti-depressants") increases adherence, while beliefs about harm, overprescribing, and fear of side effects reduces adherence.

5. Previous experiences - individuals who had a prior experience of depression and anti-depressants have better adherence now, and so having a vicarious experience of depression (ie: family member or friend) (Hung 2014).

6. Relationship with health professionals - adherence is higher when there is a good relationship with the doctor, and lower if the interactions are perceived as unsatisfactory.

7. Genes - recent research has shown a genetic basis to variability in anti-depressant response (and consequently adherence to anti-depressants).

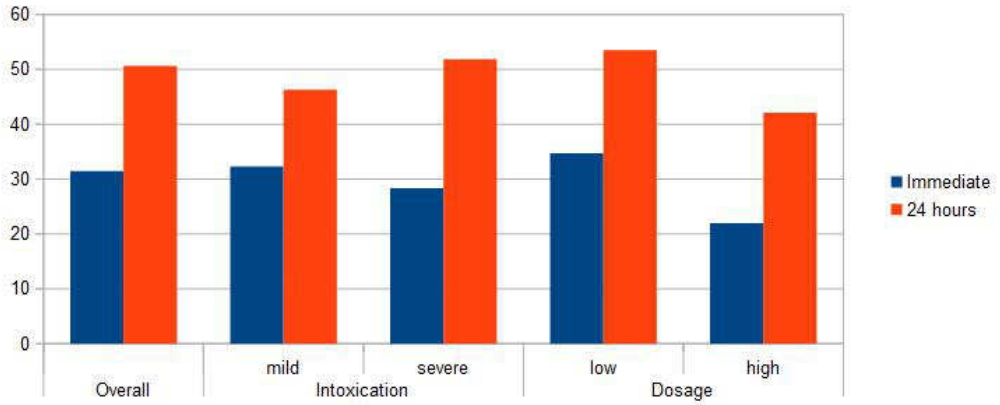
It should be noted that the above factors interact. However, "the most common reasons for early discontinuation of anti-depressant treatment are adverse effects and lack of efficacy" (Hung 2014 p348).

OVERDOSE

Overdose from tricyclic anti-depressants (TCAs) can produce short-term memory impairment. This has been shown in laboratory experiments with the deliberate injection of the substance in rats (eg: imipramine; Zarrindast et al 2003).

Such studies are not possible with humans, so real-life cases must be used. This is what Eizadi-Mood et al (2015) did at the Poisoning Emergency Department of Noor and Ali Asghar University hospital in Isfahan, Iran. The researchers had a sample of sixty-seven individuals who arrived at the hospital with TCA poisoning. These individuals underwent a standardised memory test immediately and 24 hours after waking (ie: resolution of poisoning symptoms).

The memory score was significantly lower on the immediate test than 24 hours later, which suggested "memory improvement that will improve significantly during the next 24 hours" (Eizadi-Mood et al 2015). The severity of the memory impairment depended on the drug dosage and the severity of intoxication (figure 4). The upshot was that the psychiatric assessment of the individuals is better 24 hours later than immediately on waking.



(Data from Eizadi-Mood et al 2015 table 1 p3)

Figure 4 - Mean memory scores immediately and 24 hours after waking from TCA overdose.

Table 2 summarises the main strengths and weaknesses of the study.

STRENGTHS	WEAKNESSES
1. All patients aged 20-64 years old at one hospital in a certain time period (which was not specified). 2. Exclusion of individuals with history of dementia or other diseases that affect cognitive functioning. 3. Sample divided into two groups for analysis based on severity of poisoning (less or more than 500 mg). 4. Use of standardised memory test - Wechsler Memory Scale (4th ed) (WISC-IV) - which measures immediate and delayed recall. 5. Only means to study this behaviour as an experiment is not ethical with humans (ie: deliberately giving overdose).	1. A cross-sectional study which compared the individuals at one point in time only. Also no details beyond 24 hours after waking. 2. Details of overdose as reported by relatives (ie: no verification by blood test). 3. Sample small overall, and group sizes not equal (ie: severe group, n = 15). 4. Sample from one hospital in one city limits generalisability of findings. 5. Patients who did not co-operate with the test were excluded. No details are given about these individuals.

Table 2 - Main strengths and weaknesses of Eizadi-Mood et al (2015).

APPENDIX 2 - RECRUITMENT FOR RANDOMISED CLINICAL TRIALS

Randomised clinical trials (RCTs) are the most scientifically rigorous way to test a treatment, but many trials struggle to recruit participants and to retain them. For example, up to and over 50% of privately- and publicly-funded trials require extensions due to recruitment problems (Hughes-Morley et al 2015).

Hughes-Morley et al (2015) admitted that "there is a general consensus that depression trials experience particular challenges with recruitment, and many fail to recruit their proposed sample of participants to target, or indeed fail altogether" (p275). Problems with recruitment increase costs of the trial, have the risk of less statistical power with smaller samples, and lead to delays in generating evidence (Hughes-Morley et al 2015).

Hughes-Morley et al (2015) undertook a systematic review of factors affecting recruitment into depression trials. A literature review was made for relevant studies in English up to April 2013, and fifteen studies were found to fit the inclusion criteria (eg: peer-reviewed).

Analysis of these studies produced forty-five

themes, which reduced to eleven sub-themes under two categories that covered both patients/sufferers and "gatekeepers" (eg: health professionals).

1. Barriers to participation.

i) Expression of depression symptoms - how depression affects the individual and their willingness to participant in a trial (eg: "too ill").

ii) Risk of trial to mental health - eg: anxiety about taking part. As one interviewee in a study said: "If I felt that I'd reached a stage with my depression that it was no longer a factor in a) my working life, b) my social life, c) my domestic life, then I wouldn't [participate], because you're on the straight and narrow and you don't want anything to demur from that or jeopardise it" (quoted in Hughes-Morley et al 2015 p281).

iii) Stigma of taking part.

iv) Protecting the vulnerable patient - doctors' willingness to volunteer vulnerable individuals, particularly with randomisation. "For GPs, randomisation was often a difficult procedure in practice, even though they acknowledged its value. The traditional responsibility of GPs is the well-being of individual patients, which is promoted by directing them to the best possible treatment for their presenting problems. Randomisation presented GPs with a competing responsibility, specifically, to prioritise scientific advancement from which future patients would benefit. Faced with an ethical dilemma between care of their patients and research interests, GPs often opted to adhere to their traditional role and did not risk their patient being randomised to the non-desired arm of the study" (Hughes-Morley et al 2015 p282).

v) Presenting depression trials to patients.

vi) Treatment preferences - eg: patients may have particular preferences and not want to participate in a trial with the chance that given placebo.

vii) Views of trial processes and procedures - eg: inconvenience of participation.

2. Facilitators to participate.

i) Access to services to meet mental health need - ie: extra resources offered by trial.

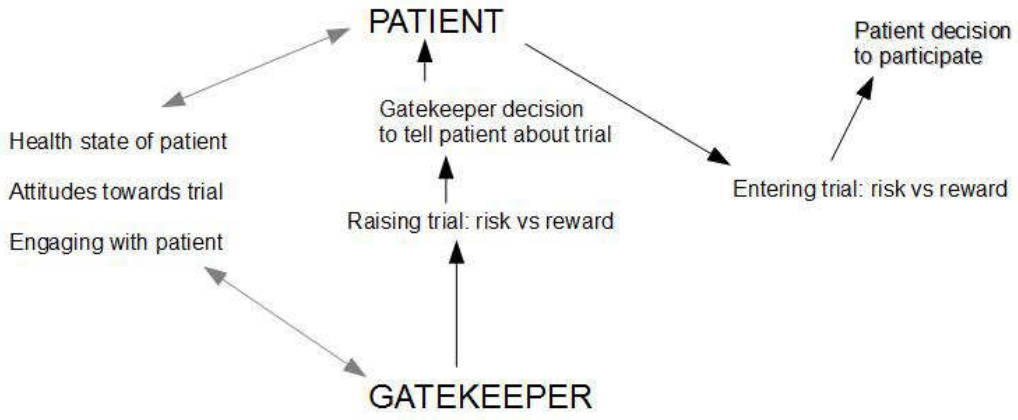
ii) Altruism.

iii) Marketing of trial to patients and "gatekeepers".

iv) Trust in individuals and organisations involved - for example, one patient in a study said: "If it was my doctor suggested it: 'will you try this?' I'd say yes, but if anybody else asked me, I would probably say no" (quoted in Hughes-Morley et al 2015 p284). Mistrust was a particular issue for older African-American individuals (Shellman and Mokel 2010).

Hughes-Morley et al (2015) summed up: "Our review highlights that the decision to enter a depression trial depends on the patient's health state at the time of the approach; on their attitude towards the interventions being evaluated within the trial; and on the extent to which patients become engaged with the trial. Our conceptual framework emphasises that the decision to participate by both the gatekeeper and the patient involves a judgement between risk and reward" (p284) [14].

The researchers conceptual framework was based a round the three constructs of health state, attitudes towards trial, and engaging the patient (figure 5).



(Based on Hughes-Morley et al 2015 figure 2 p285)

Figure 5 - Framework of factors influencing participation in depression trials.

[14] The risk and reward to participate is influenced by two concepts - therapeutic misconception and injurious misconception. The former is "an overstated sense of benefit, and occurs when participants demonstrate difficulties in appreciating the distinction between clinical treatment and research, therefore incorrectly attributing the therapeutic intent to research procedures" (Hughes-Morley et al 2015 p285), while injurious misconception is the opposite with an "overstated sense of risk and threat associated with research".

APPENDIX 3 - COVERT HETEROGENEITY

In the large clinical trial, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study [15], only one in four patients had remission of symptoms in the first stage. One explanation proposed for the "disappointing findings" is "covert heterogeneity" - ie: differences in symptoms between sufferers of major depressive disorder (MDD). Fried and Nesse (2015) noted: "The current disease category depression is commonly regarded as a consistent syndrome, justifying the use of symptom sum-scores and thresholds: the number of symptoms is the main focus, while specific symptoms are ignored. This approach, however, may obfuscate dramatic differences among depressed individuals in their endorsed symptoms" (p96).

In DSM-5 (APA 2013), diagnosis of depression requires the presence of at least five of nine symptoms (table 3), including depressed mood or diminished interest/pleasure. Fried and Nesse (2015) pointed out that "all symptoms except depressed mood are compounds that include at least two sub-symptoms, and three of the criterion symptoms (sleep, weight/appetite, psychomotor) can be met by either increases or decreases. This means that two individuals who qualify for a diagnosis of MDD may not have a single symptom in common. Taking only the nine DSM-5 criterion symptoms into account, 227 unique symptom profiles exist that all qualify for a diagnosis of MDD. Considering the extremes of sleep, appetite and psychomotor changes separately increases the number of unique profiles to 945, and taking into account sub-symptoms of all eight compounds leads to 16 400 different profiles that qualify for a diagnosis of MDD" (p97).

- Depressed mood
- Diminished interest/pleasure
- Weight/appetite increase/decrease
- Insomnia/hypersomnia
- Psychomotor agitation/retardation
- Fatigue or loss of energy
- Feelings of worthlessness or inappropriate guilt
- Diminished ability to think or concentrate, or indecisiveness
- Recurrent thoughts of death or recurrent suicidal ideation

(Source: Fried and Nesse 2015)

Table 3 - Nine symptoms of MDD in DSM-5.

[15] This is a multi-site randomised controlled trial in the USA to test different treatments for non-psychotic MDD. The first stage involved 3700 patients receiving citalopram (a selective serotonin reuptake inhibitor anti-depressant).

Fried and Nesse (2015) analysed the symptom profile of the participants in the STAR*D study, and found 1030 unique profiles. The mean number of symptoms was six, with sad mood, loss of energy, and concentration problems as most common. The most common symptom profile was shared by 2% of participants, while 14% of individuals had a unique symptom profile not shared by anybody else on the study.

The main implication of the findings was that a total score (or sum-score) for depression severity "may be unjustified. Sum-scores may provide an estimate of overall psychopathological load, but individual depression symptoms differ in their impact on impairment of psychosocial functioning..., can be more informative about global functioning than symptom sum-scores..., and depression can be very severe even when only a few symptoms are present" (Fried and Nesse 2015 p99). Also individuals with similar sum-scores could have different symptom profiles.

Fried and Nesse (2015) offered possible explanations for their findings:

i) The symptoms are interchangeable, and "unimportant because all symptoms have the same underlying cause" (p99).

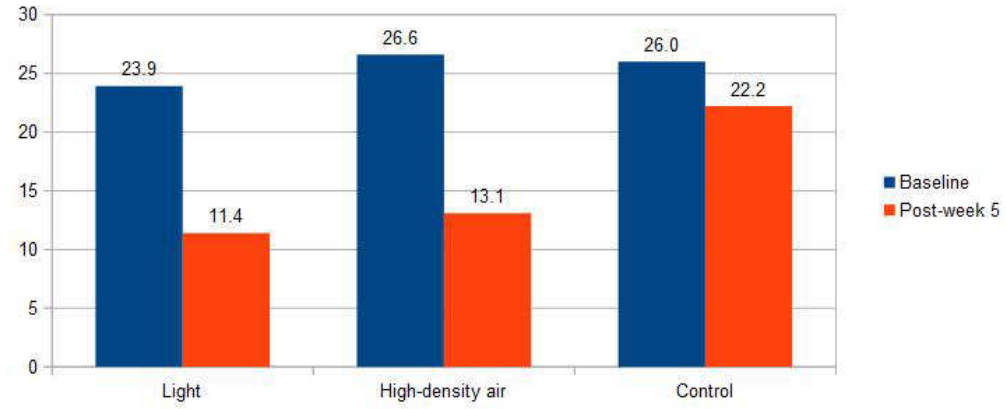
ii) Depression is actually "numerous syndromes that differ in aetiology, symptom presentation, and biological predisposition" (p99).

iii) Depressive symptoms arise from different causes - "from primary brain changes from those aroused by life situations, inflammation, or some other stimulus that normally causes low mood" (p99).

Taking elements of these ideas, Fried and Nesse (2015) argued for a network model. They said: "From a network perspective, symptoms do not cluster because of a common cause - they cluster because they are connected in complex dynamic causal networks of direct and indirect influences; insomnia may lead to fatigue, which may in turn cause psychomotor and concentration problems, irrespective of the particular diagnosis a patient may have. The network theory predicts that the reason for the higher inter-correlation within these so-called somatic depression items is not a specific disease type that causes predominantly somatic symptoms, but that a somatic symptom likely leads to other somatic symptoms that may fuel each other in vicious circles of mutual influence" (p100). So, MDD is not a single condition with one cause.

8. ALTERNATIVE TREATMENTS FOR DEPRESSION

A number of different ideas related to the environment are recommended to reduce depression. One in particular has support from evidence - bright light [16] - while another (negatively-charged atoms [17]) is not quite as well supported. However, Goel et al (2005), for example, found support for both. They treated thirty-two volunteers, who were out-patients at a New York psychiatric hospital [18], diagnosed with DSM-IV major depression lasting at least two years, with one of three options - fluorescent lamp (n = 10), "high density" ion generator (ie: negative-charged atoms) (n = 12), or "low density" ion generator (ie: no effect - control) (n = 10). The options were used for one hour every morning for five weeks. Half of the light (5/10) and "high-density" generator groups (6/12) showed remission [19] compared to none of the control group (0/10) (figure 6).



(Data from Goel et al 2005 table 1 p 949)

Figure 6 - Mean SIGH-SAD scores (out of 29).

Reminiscence, defined as "the vocal or silent recall

[16] This has been found to work with sufferers of Seasonally Affective Disorder (SAD). There are less side effects than drugs, and is appropriate for non-responders to drugs or those who cannot tolerate them (Goel et al 2005). For example, twenty studies reviewed by Golden et al (2005) showed that remission of SAD was almost three times that of placebo, but no benefits for non-seasonal depression. However, Terman (2006) noted that it was "difficult to define an appropriate inactive placebo for phototherapy. Placebo usually included some degree of light exposure in an attempt to blind participants to treatment condition" (p21).

[17] Negative air ions concentration is higher in the summer (than winter), and in humid (than dry) environments. Artificial heat and air conditioning produce increased positive air ions (Goel et al 2005).

[18] There were not taking anti-depressant medication.

[19] Remission was defined as a reduction of eight points or more from the baseline score of the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version (SIGH-SAD).

of events in a person's life, either alone or with another person or group of people", and life review ("the process of reviewing, organising and evaluating the overall picture of one's life") (Wood et al 1992 quoted in Elford et al 2005) can reduce negative mood in older adults [20]. But is it "simply a diversional activity without measurable therapeutic benefits" (Elford et al 2005)?

Five residents at a nursing home in South Yorkshire were found to benefit from writing about aspects of their lives (Elford et al 2005). One man (aged 89 years old) and four women (aged 71-84 years) were asked to write about four different aspects of their lives - childhood, neighbourhood, workdays, and holidays - over a six-month period. The writing was printed up in booklets.

Elford et al (2005) picked out the following themes from the experience:

1. Proof/maintenance of skills

a) Writing skills - eg: up to 25 sheets of A4 produced by each writer.

b) Proof of intact memory - eg: "Sarah" proud that she had not "lost" certain memories after stroke.

2. Psychological/internal processes

a) Writing cathartic - eg: "Jack" and recent loss of wife.

b) Keep busy - having a purpose - eg: stop "Jack" from being "bored most of the time".

3. Social contact

a) Sharing with others/telling their story - eg: "Emily" had her family in mind when writing.

b) Prop for social interactions - eg: "gave something to do, talk about" with relatives.

c) Communication - an alternative to verbal communication of feelings.

d) Confidante - talking to researchers during project.

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[20] In a meta-analysis of twenty studies, Bohlmeijer et al (2003) found that reminiscence and life review reduced depressive symptoms significantly better than controls. But only four studies were rated high quality by the authors, and few investigated the long-term effects.

4. Pleasure in reminiscence.

Elford et al (2005) offered a word of warning: "in encouraging people to write about their stories caution should be exercised and issues of confidentiality, audience, support and appropriateness of the activity for the individual considered" (p313).

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