



# Is the chemical imbalance an ‘urban legend’? An exploration of the status of the serotonin theory of depression in the scientific literature

Benjamin Ang<sup>a</sup>, Mark Horowitz<sup>a,b</sup>, Joanna Moncrieff<sup>a,b,\*</sup>

<sup>a</sup> Division of Psychiatry, University College London, UK

<sup>b</sup> North East London Foundation Trust, UK

## ARTICLE INFO

### Keywords:

Depression  
Serotonin  
5-HT  
Serotonin theory of depression  
Monoamine hypothesis of depression

## ABSTRACT

The theory that depression is caused by a serotonin abnormality or other chemical imbalance has become widely accepted by the public and is one prominent justification for the use of antidepressants. However, it has been increasingly questioned and there is little evidence it has empirical support. In response, leading psychiatrists suggested it was an ‘urban legend’ that was never taken seriously by the psychiatric profession. To interrogate these claims, we examined the coverage of the serotonin theory of depression in a sample of highly cited and influential academic literature from 1990, when the theory started to be popularized, to 2010 when these responses were articulated. We analysed 30 highly cited reviews of the aetiology of depression in general, 30 highly cited papers on depression and serotonin specifically and a sample of influential textbooks. The majority of the aetiology reviews supported the hypothesis, including some that were entirely devoted to describing research on the serotonin system, and those that reviewed the aetiology of depression more broadly. Research papers on the serotonin system in depression were highly cited and most of them strongly supported the serotonin theory. All textbooks supported the theory, at least in some sections, and devoted substantial coverage to it, although some also acknowledged it remained provisional. The findings suggest that the serotonin theory was endorsed by the professional and academic community. The theory is compared to an exhausted Kuhnian paradigm with professional equivocation about it acting as a means of defending it against encroaching criticism. The analysis suggests that, despite protestations to the contrary, the profession bears some responsibility for the propagation of a theory that has little empirical support and the mass antidepressant prescribing it has inspired.

## 1. Introduction

The idea that depression is caused by lowered serotonin or another brain chemical imbalance has become, in the 21st century, what France et al. (2007) described as the ‘dominant cultural story of depression aetiology’ (France et al., 2007) (P 411). Social scientist, Nikolas Rose has reflected on how this story has changed the way people think about their moods and, by extension, their very concept of themselves. As people have started to ‘recode their moods and their ills in terms of their brain chemicals,’ they have come to think of themselves as ‘neurochemical selves,’ with profound implications for their sense of agency and self-efficacy (Rose and Stehr, 2004) (P 28).

Despite this situation, leading psychiatrists have claimed that the chemical imbalance theory of the aetiology of depression is an ‘urban legend’ that was never ‘seriously propounded by well-informed psychiatrists’ (Pies, 2011a). These comments were made in response to

increasing criticism of the theory, and reflect a common medical outlook today (Eske, 2019). In this paper we present evidence that this position is patently false, and acts as a means of defending a theory that has been described as an obsolete Kuhnian paradigm (Healy, 1987) against encroaching criticism, paradoxically enabling it to survive and to continue to be influential.

### 1.1. The historical context

The chemical imbalance theory was first proposed in the 1960s (Schildkraut, 1965). At that time, interest focused mainly on the neurochemical noradrenaline, but serotonin (5-hydroxytryptamine or 5-HT) was also proposed to be relevant (Coppin, 1967). What came to be known as the ‘monoamine hypothesis’ (noradrenaline and serotonin are both classified as monoamines), was stimulated by the belief that certain prescription drugs targeted the basis of mood, particularly drugs that

\* Corresponding author. Division of Psychiatry, University College London, Gower street, London, WC1E 6BT, UK..

E-mail address: [j.moncrieff@ucl.ac.uk](mailto:j.moncrieff@ucl.ac.uk) (J. Moncrieff).

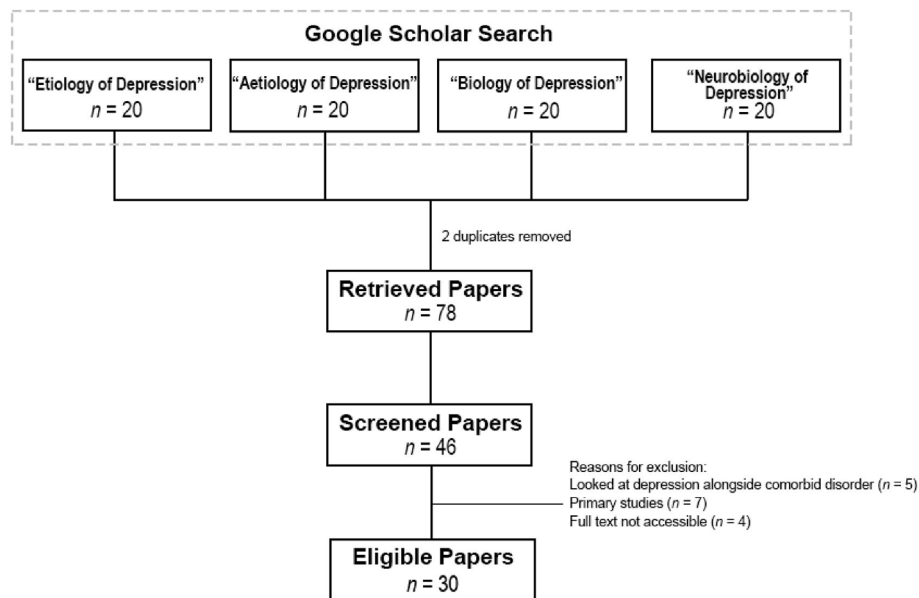


Fig. 1. Selection of aetiology of depression review papers.

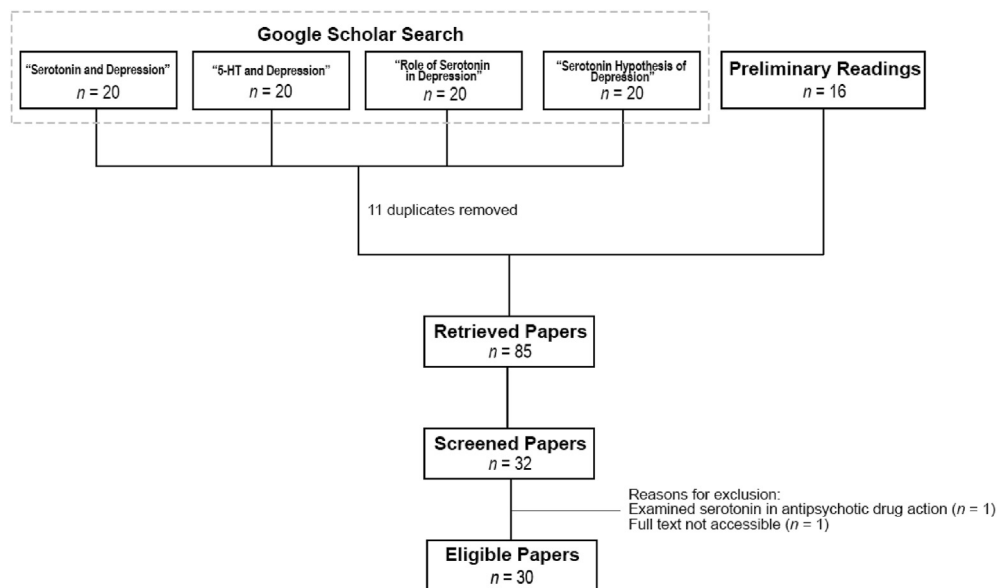


Fig. 2. Selection of serotonin 'link' papers.

**Table 1**  
Psychiatry and psychopharmacology textbooks examined<sup>a</sup>.

Subject	Country	Ed. (Year)	Title
Psychopharmacology	US	1st Ed. (1996)	Essential Psychopharmacology
Psychopharmacology	UK	2nd Ed. (2004)	Fundamentals of Clinical Psychopharmacology
Psychiatry	UK	2nd Ed. (2009)	New Oxford Textbook of Psychiatry
Psychiatry	UK	5th Ed. (1993)	Companion to Psychiatric Studies
Psychiatry	UK	2nd Ed. (2004)	Core Psychiatry
Psychiatry	US	9th Ed. (2009)	Comprehensive Textbook of Psychiatry

<sup>a</sup> Full references are provided in the supplementary information.

were named 'antidepressants' (Moncrieff, 2008a).

The serotonin version of the monoamine hypothesis, or the 'serotonin hypothesis', was further embedded in the professional and popular psyche following the introduction of the selective serotonin reuptake inhibitor (SSRI) antidepressants into the market from the late 1980s. SSRIs inhibit serotonin transporter proteins from transporting serotonin from the synaptic cleft back into the presynaptic neuron and are therefore thought to increase the availability and activity of synaptic serotonin. Throughout the 1990s and beyond, the pharmaceutical industry promoted the idea that depression was the result of an 'imbalance' or deficiency of brain serotonin, and that SSRIs were 'magic bullets' that reversed this underlying abnormality (Healy, 2015). A patient information leaflet from the 1990s, for example, informed people that 'when serotonin is in short supply, you may suffer from depression' (Valenstein, 1998) (cited on P 181). A direct-to-consumer advertisement from 2003 told consumers that 'while the cause is not known, depression may be related to an imbalance of natural chemicals between nerve cells in the

**Table 2**  
Scope of the aetiology review papers<sup>a</sup>.

Scope	Papers
Reviews a range of factors in the aetiology of depression (n = 14)	Dunn and Dishman (1991), Nemeroff (1998), Yadiid et al. (2000), Gottfries (2001), Manji et al. (2001), Wong and Licinio (2001), Nemeroff (2002), Nestler et al. (2002), Kalia (2005), Maletic et al. (2007), Shelton (2007), Krishnan and Nestler (2008), Maletic and Raison (2009), Krishnan & Nestler (2010),
Reviews a specific alternative biological hypothesis to the serotonin hypothesis (n = 7)	Licino and Wong (1999), Ehlert et al. (2001), Rice et al. (2002), Myint and Kim (2003), Gillespie and Nemeroff (2005), Sahay & Hen (2007), Castrén and Rantamäki (2010)
Reviews research on a specific aspect of the serotonin system (n = 5)	Drevets (1999), Delgado (2000), Middlemiss et al. (2002), Neumeister (2003), Uher & McGuffin (2010),
Reviews social or environmental aetiological factors (n = 4)	Price et al. (1994), Heim et al. (1997), Heim et al. (2004), Maniglio (2010)

<sup>a</sup> Full references to all the papers are provided in the supplementary information.

**Table 3**  
Support for the serotonin hypothesis among selected aetiology papers<sup>a</sup>.

Degree of support for the serotonin hypothesis	Number of papers N = 30	References
Unequivocal support for serotonin having a direct role in the aetiology of depression	11	Nemeroff, 1998; Delgado, 2000; Yadiid et al., 2000; Gottfries, 2001; Middlemiss et al., 2002; Nemeroff, 2002; Myint and Kim, 2003; Neumeister, 2003; Heim et al., 2004; Kalio, 2005; Maletic et al., 2007
Serotonin as part of the causal pathway of depression	9	Dunn & Dishman, 1991; Heim et al., 1997; Drevets, 1999; Lianio and Wong, 1999; Manji et al., 2001; Shelton, 2007; Krishnan & Nestler, 2008; Maletic & Raison, 2009; Uher and McGuffin, 2010
Suggestive support for the serotonin hypothesis	1	Wong and Licinio, 2001
Discounts the serotonin hypothesis	1	Krishnan and Nestler, 2010
Ambiguous	1	Nestler et al., 2002
Not covered	7	Price et al., 1994; Ehlert et al., 2001; Rice et al., 2002; Gillespie and Nemeroff, 2005; Sahay and Hen, 2007; Maniglio, 2010; Castren and Rantamaki, 2010

<sup>a</sup> Full references are provided in the supplementary information.

brain' and that 'prescription Zoloft works to correct this imbalance' (Pfizer. Zoloft advertsiement, 2004) (cited in Lacasse and Leo, 2005).

This message was propagated on popular websites (Demasi and Gotzsche, 2020), and best-selling books, such as *Listening to Prozac* (Kramer, 1993), spread the news of the apparently miraculous effects of SSRIs, which appeared to confirm the serotonin theory. Professional organisations, such as the American Psychiatric Association echoed drug company rhetoric, suggesting in a patient leaflet produced in 2005 that 'antidepressants may be prescribed to correct imbalances in the levels of chemicals in the brain' (American Psychiatric Association, 2005). Consequently, a large proportion of the population came to believe that depression is caused by a 'chemical imbalance', with surveys conducted in the 2000s finding that 88% of respondents in Australia and 85% in the US endorsed this idea (France et al., 2007; Pilkington et al., 2013).

The marketing of the SSRIs and the associated serotonin theory of

**Table 4**  
Support for the serotonin hypothesis among selected serotonin 'link' papers<sup>a</sup>.

Degree of support for the serotonin hypothesis	Number of papers N = 30	References
Unequivocal support for serotonin having a direct role in the aetiology of depression	16	Owens and Nemeroff, 1994; Maes and Meltzer, 1995; Artigas et al., 1996; Graeff et al., 1996; Ogilvie et al., 1996; Lucki, 1998; Stockmeier et al., 1998; Drevets et al., 1999; Ressler and Nemeroff, 2000; Young and Leyton, 2002; Blier and Ward, 2003; Celada et al., 2004; Eley et al., 2004; Mollwer and Schwartz, 2007; Seo et al., 2008; Maes et al., 2009
Serotonin as part of the causal pathway of depression	6	Altar, 1999; Holsboer, 2000; Kaufman et al., 2004; Groves, 2007; Maes, 2008; Uher and McGuffin, 2010
Suggestive support for the serotonin hypothesis	4	Hirschfeld, 2000; Svenningsson et al., 2006; Ruhe et al., 2007; Savitz et al., 2009; Lacasse and Leo, 2005
Discounts (challenges) the serotonin hypothesis	1	
Ambiguous	1	Risch et al., 2009
Not covered	2	Kirsch et al., 2002; Whittington et al., 2006

<sup>a</sup> Full references are provided in the supplementary information.

depression has been paralleled by an extraordinary increase in the use of antidepressants all over the world. Prescriptions of antidepressants in England increased three times between 1988 and 1998 (Middleton et al., 2001) and more than tripled again from 1998 to 2018 (Bogowicz et al., 2021). By 2017, 17% of the population of England were prescribed an antidepressant (Taylor et al., 2019). Prescriptions have been rising throughout Europe over the same period, with some countries in Eastern Europe, where use was previously low, showing increases of 5–6 times since 2000 (Organisation for Economic Co-Operation and Development, 2020). In the United States, antidepressant prescriptions increased over 4 times between the late 1980s and the mid-2000s (Wehrwein, 2011) and have continued to increase (Mojtabai and Olfson, 2010). Data from China shows prescriptions have risen across the country in recent years (Yu et al., 2020). Evidence also indicates that increasing numbers of people are taking antidepressants on a long-term basis (Taylor et al., 2019; Mojtabai and Olfson, 2010). Research confirms that the belief that depression is due to a 'chemical imbalance' is widespread among antidepressant users and can encourage people to ask for antidepressants, and prevent people from trying to stop them (Read et al., 2015; Cohen and Hughes, 2011; Eveleigh et al., 2019).

### 1.2. Debate and controversy in the 21st century

Despite widespread public acceptance, the 21st century saw increasing debate about the serotonin theory of depression within professional, academic and popular fora. In 1987, Irish psychopharmacologist, David Healy, was already describing how evidence did not support the amine theory of depression, either in relation to noradrenalin or to serotonin (Healy, 1987). In his 1997 book *The Antidepressant Era*, he concluded that 'no abnormalities of either catecholamine or 5HT (serotonin) systems have ever been replicated in a manner that has commanded widespread support' (Healy, 1997) (P 159). Critics also pointed to the lack of evidence to support the serotonin theory of depression (Valenstein, 1998; Breggin, 1997), but these views did not reach peer reviewed journals or mainstream media outlets or make an impression on what passed for general psychiatric knowledge before the 2000s.

In 2005, two American academics, Jeffrey Lacasse and Jonathan Leo, published a paper detailing the 'disconnect' between pharmaceutical

company advertising and the official position on the serotonin theory (Lacasse and Leo, 2005). The paper was published in a widely read online medical journal, *PLOS Medicine*, newly set up by the ex-editor of the British Medical Journal (BMJ). The authors compared the messages commonly presented in advertisements, which emphasised the idea that depression is caused by a chemical imbalance corrected by antidepressants, with statements by academics and researchers claiming that the serotonin theory of depression was unsupported or unproven. The latter were mostly voiced by established critics of biological psychiatry, such as Elliot Valenstein, but some came from more mainstream figures.

The article received considerable attention, because it was the first time the media had wind of the possibility that the serotonin theory might not be supported by evidence. It provoked a defensive response from some leading psychiatrists. Wayne Goodman, academic psychiatrist and chair of the FDA psychopharmacological committee, admitted that evidence of a neurochemical deficiency in people with depression was 'elusive', but described the chemical imbalance as a 'useful metaphor,' although not one he would use with his own patients (Anonymous, 2005). However, he still asserted that depression 'is a chemically or brain-based problem and that the medications are normalizing function,' and maintained that the idea of a chemical imbalance was a 'reasonable shorthand' to describe this situation (Meek, 2006).

In 2011, Ronald Pies, editor-in-Chief Emeritus of *Psychiatric Times* and one of America's most prestigious psychiatrists, responded to a report published by the Citizens Commission on Human Rights (CCHR, a Church of Scientology organisation) in a similar vein. It was in this article that he dubbed the chemical imbalance theory of depression an 'urban legend' and claimed that no well-informed psychiatrist had ever believed it, since they understood the true biopsychosocial nature of mental disorders. Unfortunately, he continued, this had not been widely understood, and 'opponents of psychiatry mendaciously attribute the phrase to psychiatrists themselves'. According to Pies, the theory had been propagated by the pharmaceutical industry alone, and should be 'consigned to the dust-bin of ill-informed and malicious caricatures' (Pies, 2011a).

A few months later, apparently in reply to a confused reader, and most likely in response to people protesting that they had, indeed, been told by a psychiatrist that they had a chemical imbalance, he confessed that many psychiatrists do use the chemical imbalance explanation. He went on to claim, however, that psychiatrists don't fully believe it, so they 'feel uncomfortable and a little embarrassed' when they do so. They only use it, apparently, to make their patients feel better, and to save time. Having said this, Pies went on to distinguish between what he characterized as a crude and mistaken theory of chemical imbalances, and the more sophisticated and nuanced 'biogenic amine hypothesis' that holds that depression is partially caused by neurochemical abnormalities in conjunction with other factors (Pies, 2011b).

In 2014 Pies repeated this position along with the accusation that 'antipsychiatry' groups had wrongly propagated the idea that 'a monolithic entity called "Psychiatry" has deliberately misled the public as to the causes of mental illness, by failing to debunk the chemical imbalance hypothesis' (Pies, 2014). In 2015, he responded to a further article by Lacasse and Leo making similar points (Pies, 2015). However, another psychiatrist, Daniel Carlat, responding to the same article, declared that he told patients that antidepressants work by 'rebalancing' brain chemicals, and denied that there was any serious doubt about the serotonin theory of depression: 'while we don't understand exactly what serotonin's role is ... it is clear that effective antidepressants exert their actions via shifts in the brain's biochemical milieu- and that serotonin is one of the central players in the drama' (Carlat, 2015).

### 1.3. Current ideas

The debate about whether or not the serotonin theory was promoted by the psychiatric profession has continued. Critics of psychiatry have repeatedly asserted that the profession misled the public (Hickey, 2021; Fennell, L. & Bradshw, M. *When doctors mislead; the chemical imbalance*

lie. 2016. Available from <https://davidhealy.org/wp-content/uploads/2016/06/When-doctors-mislead-the-chemical-imbalance-lie.pdf>. Accessed 10th Dec 2021), and Pies has continued to claim that the profession was not responsible for promoting the theory (Pies, 2019). Psychiatrist, David Healy, also argued that the 'lowered serotonin story took root in the public domain rather than in psychopharmacology' and that researchers only used the 'language' of lowered serotonin as a 'form of a symbol referring to some physiological abnormality that most still presume will be found to underpin melancholia—although not necessarily primary care "depression"' (Healy, 2015) (P 1). However, Healy also acknowledged that the serotonin myth had 'co-opted doctors and patients' and plenty of evidence now confirms that doctors used the idea of an underlying chemical imbalance or serotonin abnormality to justify the prescription of antidepressants (Cohen and Hughes, 2011; Read et al., 2020).

To this day, there is no definitive, accepted position on the serotonin theory of depression, but no consistent evidence of an association between markers of reduced serotonin activity or concentration and depression has been found (Moncrieff, J.; Cooper, R.; Stockmann, T.; Amendola, S.; Hengartner, M.P.; Horowitz, M.A. *The serotonin theory of depression: a systematic umbrella review of the evidence*. Manuscript submitted for publication.). The efficacy of antidepressants has also been questioned by numerous researchers who have shown that the differences between antidepressants and placebo are marginal, unlikely to be clinically significant and plausibly explained by factors other than the presumed therapeutic, pharmacological effects (Jakobsen et al., 2019; Munkholm et al., 2019). Several authors have highlighted how mind-altering drugs, including antidepressants, can affect mood and other mental faculties without targeting a disorder-specific biological mechanism (Breggin, 1997; Moncrieff and Cohen, 2005). Therefore, the mode of action of a drug does not necessarily indicate anything about the biology of the condition it is used to treat. Although there remain plenty of advocates for antidepressants, the media has paid increasing attention to evidence suggesting they are over-used and potentially harmful, including stories of those who have suffered from severe and protracted withdrawal symptoms after trying to stop antidepressants (Carey, B. & Gebeloff, R. *Many People Taking Antidepressants Discover They Cannot Quit*. *New York Times*, 7th April 2018). People who have been harmed by antidepressants have been critical of the overprescribing of these drugs and the propagation of the 'serotonin myth' (Fennell, L. & Bradshw, M. *When doctors mislead; the chemical imbalance lie*. 2016. Available from <https://davidhealy.org/wp-content/uploads/2016/06/When-doctors-mislead-the-chemical-imbalance-lie.pdf>. Accessed 10th Dec 2021; Fox D., *A Worldwide Epidemic – the Misuse of Anti-depressant Medications* 2016. Accessed 13th Oct 2021. Available at <https://www.madinamerica.com/2016/05/a-worldwide-epidemic-the-misuse-of-anti-depressant-medications/>). In a 2015 article in the *BMJ*, David Healy described the serotonin theory as a 'myth' and an example of 'neurobabble,' whose influence and popularity was attributable to marketing rather than science (Healy, 2015).

Much psychiatric opinion now follows Pies' lead and expresses the view that the idea that depression is caused by brain chemical imbalances is an 'over-simplification' that should not be taken too seriously (Eske, 2019; Pariante, 2018; Royal College of Psychiatrists, 2019). On the other hand, some psychiatrists continue to defend the serotonin hypothesis of depression (Harmer and Cowen, 2018) and Pies himself still promotes the monoamine hypothesis in a form that has apparently been 'modified and corrected to reflect more complex biological mechanisms in major mood disorders' (Pies, 2019). Public information, including that produced by psychiatric organisations like the APA, continues to suggest that 'differences in certain chemicals in the brain may contribute to symptoms of depression' and antidepressants are still presented as correcting chemical imbalances (American Psychiatric Association, 2021). Thus, current attitudes reflect the paradoxical situation in which the chemical imbalance theory of depression is simultaneously endorsed and disowned.

## 2. Aims

The early history of the serotonin hypothesis has been well-documented (France et al., 2007; Moncrieff, 2008a; Lopez-Munoz and Alamo, 2009), but subsequent events are less clear. In particular, the extent to which professional psychiatry and the research community accepted and propounded the theory remains uncertain. In the light of recent debate, the current project aimed to clarify the extent of support for the serotonin hypothesis within the scientific and professional literature at the height of its popularity. We aimed to establish whether the serotonin theory was indeed an ‘urban legend’ that was never endorsed by the psychiatric community, or whether it was viewed as a credible scientific theory deemed worthy of investigation and dissemination.

We undertook an exploration of the scientific literature between 1990 and 2010 using contemporary sources. Prozac was launched in the late 1980s, and by 1990 the SSRIs were making significant inroads into the depression market. During the first decade of the 21st century the serotonin hypothesis came under increasing attack. The 1990s and 2000s can therefore be viewed as the period when the serotonin hypothesis was at its peak popularity and influence.

David Healy referred to the monoamine hypothesis as a defunct Kuhnian paradigm in the 1980s and speculated that it had remained influential because it satisfied the need for a neat and compelling biological explanation of depression (Healy, 1987). In the light of our findings, we consider how the serotonin theory might serve the interests of doctors and researchers and how, paradoxically, disclaiming the theory may enable it to survive.

## 3. Methods

Two main types of source material, academic journal articles and textbooks, were identified to capture beliefs about a serotonin-oriented explanation of depression held by members of the psychiatric community.

### 3.1. Journal articles

Two types of journal article were identified to be included: reviews of the aetiology or biological aetiology of depression and papers that examine the link between serotonin and depression specifically (‘link’ papers). The former provide an overview of the attention and emphasis given to the serotonin hypothesis or serotonergic factors among all potential causes of depression. The latter indicate the nature of research that has specifically investigated links between serotonin and depression, its conclusions and its degree of influence. In both cases, we selected the top 30 most highly cited papers that fulfilled our inclusion criteria.

Papers were identified using Google Scholar. Google Scholar’s search algorithm uses a ‘relevancy ranking’ function that sorts results both by relevance and the number of times cited, offering a good compromise between the two. The aetiology of depression review papers were retrieved using the search terms “aetiology of depression”, “etiology of depression”, “biology of depression” and “neurobiology of depression”. The search terms used to identify papers examining the serotonin ‘link’ papers were: “serotonin and depression”, “5-HT and depression”, “role of serotonin in depression” and “serotonin hypothesis of depression”.

In order to obtain a sample of the 30 most highly cited and relevant papers of each type, the first 20 results from Google Scholar using each search term were retrieved, resulting in a pool of 80 papers for each category. In addition, 16 ‘link’ papers identified during preliminary surveys of the literature were included in the pool and their citation counts retrieved from Google scholar. Duplicate papers were removed, and the remaining papers were ranked manually according to citation count. The papers were screened for eligibility in rank order until a sample of 30 eligible papers was identified. Inclusion criteria consisted of:

1. Papers in the English language
2. Papers published between 1990 and 2010
3. A citation count of at least 100
4. Primary diagnosis of interest was depression or a subtype of depression (e.g. major depressive disorder, adolescent depression etc.)
5. Papers consisted of reviews (for the aetiology review papers only)

Papers were excluded if they examined depression associated with another primary condition (except for anxiety disorders or unless a section of the paper was specifically dedicated to examining depression independent of the primary condition). Decisions about inclusion were discussed within the author team to achieve a consensus when there was confusion. The first 30 papers ordered by citations that satisfied the eligibility criteria for ‘link’ papers and aetiology papers were selected for inclusion (see Figs. 1 and 2).

All included papers were read thoroughly by the first author and checked by one of the other two authors to identify the degree of support presented for the serotonin hypothesis. All differences of interpretation were discussed among all the authors and agreement reached. The papers might explicitly propose that serotonergic mechanisms have a causal effect on depression or support the hypothesis at an implicit level, which was inferred from the manner in which links between serotonergic factors and depression were described. The strength of support for the serotonin hypothesis was gauged depending on whether the paper posited that a causal relationship between serotonin and depression had been demonstrated or was well-supported, either on its own or in conjunction with other factors, whether it presented the hypothesis as a possibility that was in need of confirmation, or whether the hypothesis was not covered, challenged, discounted or refuted.

### 3.2. Textbooks

A selection of well-known psychiatry and psychopharmacology textbooks published between 1990 and 2012 in the UK and US, were identified. UK and US textbooks were chosen as being influential, accessible and in English. Textbooks provide a snapshot of the accepted state of official knowledge at a particular point in time, and are influential as reference works and sources of education for those entering the field. Included textbooks are listed in Table 1.

In addition to describing the content of the coverage of serotonin and depression in each textbook, we compared the proportion of the textbook dedicated to the discussion of serotonergic factors with the coverage of other causal factors.

## 4. Results

### 4.1. Aetiology review papers

Fig. 1 shows the selection process for the 30 included reviews on the aetiology of depression. Table 2 summarizes the principal aims and scope of each paper. They were all highly cited with citations ranging from 3432 to 115 and a mean of 607 ( $SD = 710$ ). The role of the serotonin or the wider monoamine hypothesis was explicitly discussed in 23 of the papers, five of which were devoted entirely to aspects of the serotonin system. Only seven did not mention it at all, two of which were focused on the role of environmental factors in the aetiology of depression.

As presented in Table 3, 11 papers unequivocally supported the serotonin hypothesis of depression, claiming there was ‘overwhelming evidence’ of serotonin deficiency in depression (Nemeroff, 2002), ‘substantial indirect evidence’ (Delgado, 2000), and that the theory is ‘corroborated’ and ‘well-established’ (Middlemiss et al., 2002).

Another nine papers proposed that serotonin abnormalities were not the primary cause of depression, but are part of the causal pathways by which depressive symptoms are produced. Many of these papers stressed that depression is caused by an interaction of a multiplicity of factors in a ‘complex dysregulation of inter-related neurotransmitter systems and

distributed brain networks' (Maletic and Raison, 2009), or a 'complex interaction of multiple-susceptibility' (Sahay and Hen, 2007), and acknowledged the inconsistencies of the research on serotonin function. Most nevertheless suggested that serotonin abnormalities mediate depressive symptom production or effects of antidepressants. Three implicated serotonin in the mechanism whereby stress effects mood (Dunn and Dishman, 1991; Heim et al., 1997; Licinio and Wong, 1999) and one cited the involvement of serotonin as corroborating evidence for the effects of inflammatory processes associated with stress (Licinio and Wong, 1999). One concerned evidence on the serotonin transporter (SERT) gene and environmental adversity, concluding that previous negative findings might be accounted for by use of particular methods (Uher and McGuffin, 2010).

One paper explicitly discounted the serotonin hypothesis (Krishnan and Nestler, 2010). The authors noted there is 'little evidence' to implicate deficits of serotonin or other neurotransmitters in the aetiology of depression, and instead reviewed biological research from a diverse array of other areas. They also acknowledged 'there is no a priori reason that the mechanisms of action of a treatment is the opposite of disease pathology' (P 1307), although throughout the rest of the article antidepressants were portrayed as acting by modifying the presumed biological basis of depression at some level. However, in a previous paper, the same authors proposed that although serotonin deficiency should not be viewed as the primary cause of depression, the serotonin system is nevertheless involved in the mechanisms of antidepressant action, and this was suggested to provide an indication of the aetiology of depression (Krishnan and Nestler, 2008). An earlier paper, published by one of the authors in 2002, which is the most highly cited of all the aetiology papers with 3432 citations, was ambiguous in relation to the role of serotonin. The paper refers to the complexity of the research on antidepressant action, particularly how antidepressants are thought to have delayed effects on mood but immediate effects on neurotransmitter levels, but goes on to conclude that this indicates that 'some gradually developing neuroadaptation' to the increased neurotransmitter levels 'would appear to mediate drug action,' suggesting the serotonin system is still considered the basis of drug action (P 15).

#### 4.2. Papers on serotonin

Fig. 2 shows the selection process for the 30 included serotonin 'link' papers.

The 30 eligible papers on serotonin were more highly cited on average than the aetiology reviews, with an average of 824 citations ( $SD = 444$ ) per paper, ranging from 2413 to 403 citations. A previous study defined citation classics as publications with at least 400 citations, and only found 243 papers in the whole field of major depression that met such a criteria (Lipsman and Lozano, 2011). Therefore all the serotonin 'link' papers were highly cited and likely to be influential.

Although they were selected to represent research on serotonin, six of these papers did not focus on the serotonin system primarily, but discussed the role of the system in relation to other biological factors. Two of the papers were reviews of antidepressant studies, neither of which discussed the serotonin theory of depression per se, and one of the papers was the aforementioned critique of the serotonin hypothesis by Lacasse & Leo (Lacasse and Leo, 2005). Of the remaining papers, eight reported research on serotonin receptors in depression, seven discussed the role of the serotonin system in depression in general, five examined the serotonin transporter gene or gene-environment interactions in the context of depression and two presented evidence on other markers of the serotonin system. Notably, some of the papers were reviews of aspects of the serotonin system in the aetiology of depression that were not retrieved through the aetiology searches and one paper on the serotonin transporter gene appeared in both samples of papers (Uher and McGuffin, 2010).

Table 4 indicates the degree of support for the serotonin theory of depression across this sample of papers. Most papers presented strong

support for the theory that serotonin is involved in the pathophysiology of depression, either directly or as part of a causal pathway involving other systems. Although several papers stressed the complexity of the area, with statements such as: 'complex emotional states cannot be reduced to imbalances of a single neurotransmitter' nevertheless the association between serotonin and depression was said to be 'generally acknowledged' (Graeff et al., 1996) (P. 129), of 'special importance' (Maes and Meltzer, 1995) (P. 943) and supported by 'abundant evidence' (Ressler and Nemeroff, 2000) (P. 2). One paper referred to the association between serotonin abnormalities and depression as a 'textbook truism' (Maes et al., 2009) (P. 28).

Four papers were less emphatic and stressed how research was inconclusive or 'enigmatic' (Svenningsson et al., 2006) (P. 77), but still suggested that serotonin might be, or was 'probably' (Ruhe et al., 2007) (P. 354) involved in the aetiology of depression. One paper was ambiguous. Risch et al. (2009) (Risch et al., 2009) found no evidence that the SERT gene, either on its own or in interaction with negative life events was associated with depression, but the authors drew no conclusions about the relationship between serotonin and depression.

#### 4.3. Textbooks

All the textbooks acknowledged that the serotonin hypothesis is ultimately a hypothesis and not necessarily proven, and some stressed the complexity of the nervous system and the provisional nature of research findings on the biological basis of depression. *The New Oxford Textbook*, for example states that 'We are still a long way from understanding, with any precision, the critical connections and cellular mechanisms' (Gelder et al., 2009) (P. 663). Nevertheless, all the textbooks devoted considerable space to describing the serotonin system, how it might be involved in the aetiology of depression, the action of antidepressants drugs on serotonin, and evidence that supports the role of serotonin in depression. Three textbooks gave roughly equal attention to serotonin or serotonergic factors compared to other neurotransmitters and factors in the aetiology of depression. Two devoted a disproportionately greater amount of text to the role of serotonin and one, Stephen Stahl's *Essential Psychopharmacology*, devoted almost the entire section on the biological basis of depression to monoamines, including serotonin (Stahl, 1996).

As well as the extensive coverage of the theory, all six of the textbooks provided some degree of support or endorsement for the hypothesis. The leading US textbook of psychiatry stated unequivocally that 'the importance of NE [noradrenalin or norepinephrine] and 5-HT [serotonin] neurotransmission in the pathophysiology and treatment of mood disorders remains unquestioned.' (Sadock et al., 2009) (P. 1670). Research on genetics, hormones, the stress response and antidepressant effects were described as pointing to serotonin perturbations as the 'central disturbance' in depression, and it was suggested that a variety of research methods point to 'abnormalities of monoamine neurotransmission' or '5-HT dysfunction' (P. 1670–1671).

Stephen Stahl's textbook acknowledged that some research on serotonin has 'mixed and sometimes confusing results' (Gelder et al., 2009) (P. 122), and that the action of some antidepressants is inconsistent with the serotonin or monoamine theory, but then presented these systems in detail as being the basis of depression and the action of antidepressants.

Three of the four British textbooks downplayed the role of serotonin in some sections of the text, yet explicitly supported the hypothesis in other places. One of these, *Companion to Psychiatric Studies*, suggested in an early chapter on clinical psychopharmacology, that it 'would seem prudent from a clinical perspective to view the amine hypothesis as a set of working proposals that provide for the testing of certain essentially therapeutic models' (Johnstone et al., 1998) (P. 102). However, in a subsequent chapter on 'mood disorders', written by another author (Guy Goodwin, a well-known biologically-oriented British psychiatrist) it was claimed that genetic research, particularly research on the serotonin transporter gene, will 'confirm the role of particular neurotransmitters and their receptors for mood disorder.' (P. 412) and tryptophan depletion

studies are cited as providing 'very important confirmation of the 5 H T (serotonin) hypothesis' (P. 416). Numerous references were also made to the idea that antidepressants confirm the role of serotonin in the aetiology of depression and constitute 'a powerful argument that reduced serotonergic function is a central abnormality in mood disorder and that its correction leads to clinical response.' (P. 416).

*The New Oxford Textbook* suggested that the 'monoamine theory, is at its best, a theory about drug action' and acknowledged that 'monoamine and metabolite changes produced by illness in patients have proved remarkably unconvincing' (Gelder et al., 2009) (P. 662). However, later on the same page it claimed that tryptophan depletion studies provide evidence 'that 5-HT is intimately involved in mood disorder' (P. 662). A little later it stated that 'the function of monoamine neurons generally, and of serotonergic projections in particular, is closely associated with mood regulation.' (P. 663).

*Fundamentals of Clinical Psychopharmacology*, is the most equivocal of the textbooks examined. It highlighted how 'the hypothesis does not explain satisfactorily the similarity in efficacy of very different agents [antidepressants] acting differentially on monoamine systems. Furthermore, evidence for primary monoamine disturbance in depressed subjects is limited and inconsistent' (Anderson and Reid, 2004) (P. 60). It also pointed out that 'The action of antidepressants on monoamine neurotransmission does not by itself mean that these systems are abnormal in depression.' (P. 61). However, antidepressants were assumed to be an effective treatment for depression, and since the serotonin-related action of antidepressants was covered in detail and no other mechanisms were suggested, the implication is that they work by targeting an underlying abnormality of serotonin. Moreover, depression was listed as being associated with serotonin in a Table that presented the main neurotransmitters and disorders they are thought to be related to (P. 5).

## 5. Discussion

The idea that depression is caused by neurochemical abnormalities, and specifically an abnormality of the serotonin system, has become widely known and accepted over the last few decades since the introduction of the SSRI antidepressants. However, there has been an increasingly heated debate about it within some circles.

In 2005, Lacasse and Leo claimed that 'there exists no rigorous corroboration of the serotonin theory, and a significant body of contradictory evidence' and that 'doubts about the serotonin hypothesis are well acknowledged by many researchers'. This paper shocked the media establishment, which up until that point, had, like much of the general public, been persuaded that depression had been scientifically demonstrated to be caused by a deficiency or abnormality of serotonin. In response to the coverage, leading psychiatrists claimed that the theory was never accepted within professional or scientific circles anyway, and only ever a useful device or metaphor for persuading patients that depression is likely to have a biological basis (Meek, 2006; Pies, 2011a).

On the contrary, from our research it is clear that during the period 1990–2010 there was considerable coverage of, and support for the serotonin hypothesis of depression in the psychiatric and psychopharmacological literature. Many of the most highly cited reviews of the aetiology of depression endorsed the hypothesis, including some that were entirely devoted to describing research on the serotonin system, and those that reviewed the aetiology of depression more broadly. Research papers on the serotonin system had very large numbers of citations, and most strongly supported the serotonin theory, with a smaller number highlighting inconsistencies in the evidence and adopting a more cautious tone. Textbooks, too, though taking a more nuanced line in places, at other points presented unequivocal support for the theory.

It is true that the serotonin theory of depression was not the only focus of research or discussion on the aetiology of depression. Other biological theories such as the role of the stress hormone system were more frequently covered in reviews of the aetiology of depression, and

environmental causes or risk factors were also addressed. Many papers suggested that serotonin dysfunction was part of a complex etiological pathway, involving other biological systems. Moreover, some papers may have been written by medical writers (although there is no indication to this effect in the published articles) or cited by medical writers of other papers, contributing to their citation index. Therefore, it is possible that claims about serotonin made in some papers may reflect marketing techniques to maximise the profile of the serotonin theory. This, in turn, might explain why proclamations by representatives of the psychiatric profession were not aligned with the contents of the academic literature. Nevertheless, it is still the case that the serotonin theory was presented as a credible hypothesis supported by evidence during this period.

### 5.1. An exhausted Kuhnian paradigm

Despite the re-ignition of serotonin research by the introduction of the SSRI antidepressants in the 1990s, results remain inconsistent and overall there is no convincing evidence of serotonin system abnormalities in people with depression (Moncrieff et al, manuscript submitted for publication).

In 1987, Healy described the neurochemical theory of depression as an exhausted Kuhnian paradigm, perpetuated because it served the professional purpose of convincing patients that depression is a biological condition (Healy, 1987). Since then, the vast resources of the pharmaceutical industry have enabled the idea that depression is a biochemical condition to be deeply implanted in the public psyche. The success of this endeavor has obscured the resistance associated with alternative ways of understanding depression. The idea of the chemical imbalance and serotonin deficiency had to replace people's deeply rooted common-sense view of depression as an understandable human reaction, rather than a disease (Conneely et al., 2019). Moreover, qualitative research shows that even when people express the view that depression is a biological condition, they remain ambivalent and conflicted about it (Barr and Rose, 2008). When it comes to recovery, people usually talk in language that emphasises non-medical understandings of depression such as the need for agency and the possibility of personal change (Conneely et al., 2019; Fullagar and O'Brien, 2013). Similarly, despite evidence that the public endorses the chemical imbalance theory of depression, surveys also demonstrate that the majority of people who have been depressed favour a psychological or social explanation for depression over a biological one and prefer to have psychological therapy rather than take antidepressants (van Schaik et al., 2004; Prins et al., 2008).

In the light of the interests the theory subserves, the attempt by leading psychiatrists to deny that it was ever influential can be understood as a tactic whereby criticism can be deflected, and the theory, in some marginally modified version, can continue to be accepted. Thus, Pies, despite criticizing the supposedly simplistic notion that mental disorders are caused by 'chemical imbalances', wrote approvingly of the original monoamine hypothesis and concluded that 'certain psychiatric illnesses probably involve abnormalities in specific brain chemicals; and ... by using medications that affect these chemicals, we often find that patients are significantly improved' (Pies, 2011b). The textbooks examined here mirror this pattern, as well as recent publications on depression that often disclaim the theory while simultaneously setting it out as if it were established fact (Eske, 2019; Pariante, 2018).

A related technique could be referred to as 'moving the goalposts,' whereby when one area of research fails to produce confirmatory abnormalities, interest switches to another area (Cohen & Hughes, 2011; Healy, 1987). In this way, the chemical imbalance theory is impossible to refute and the theory is never rejected. The 'search for the elusive material substrate can continue as before without pausing to acknowledge failure' (Cohen & Hughes, 2011) (P. 183) and the market for antidepressants and the professional establishment it sustains can continue unperturbed (Moncrieff, 2008b).

Our research provides evidence that the psychiatric profession acted

as a willing and often enthusiastic conduit of the serotonin theory of depression, despite the protestations of Pies and others. Contra Pies, the profession must bear some responsibility for propagating an unsupported theory and the mass use of antidepressant drugs that has accompanied it, with all the problems that has produced.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ssmh.2022.100098>.

### References

- American Psychiatric Association. (2005). *Lets Talk Facts about Depression*. American Psychiatric Association. Available from: [www.healthyminds.org/multimedia/depression.pdf](http://www.healthyminds.org/multimedia/depression.pdf). (Accessed 13 February 2006).
- American Psychiatric Association. (16th Nov 2021). *Depression 2021*. Available from: <https://www.psychiatry.org/patients-families/depression/what-is-depression>.
- Anderson, I. M., & Reid, I. C. (2004). *Fundamentals of Clinical Psychopharmacology* (second ed.). Oxford: Taylor & Francis.
- Anonymous. (2005). Television adverts for antidepressants cause anxiety [Internet] *New Sci*. 12th October 2021; 2525(9th November 2005). Available from: <https://institutions.newsscientist.com/article/mg18825252-500-television-adverts-for-antidepressants-cause-anxiety/>.
- Barr, M., & Rose, D. (2008). The great ambivalence: factors likely to affect service user and public acceptability of the pharmacogenomics of antidepressant medication. *Sociol. Health Illness*, 30(6), 944–958.
- Bogowicz, P., Curtis, H. J., Walker, A. J., Cowen, P., Geddes, J., & Goldacre, B. (2021). Trends and variation in antidepressant prescribing in English primary care: a retrospective longitudinal study. *BJGP Open*, 5(4).
- Breggin, P. R. (1997). *Brain Disabling Treatments in Psychiatry: Drugs Electroshock and the Role of the FDA*. New York: Springer Publishing Company.
- Carey BG, R. (2018). *Many People Taking Antidepressants Discover They Cannot Quit*. New York Times.
- Carlat, D. J. (2015). Response to Lacasse & Leo. *Behav. Therapist*, 38, 262.
- Cohen, D., & Hughes, S. (2011). How do people taking psychiatric drugs explain their 'chemical imbalance?'. *Ethical Hum. Psychol. Psychiatry*, 13, 176–189.
- Conneely, M., Higgs, P., & Moncrieff, J. (2019). *Medicalising the Moral: the Case of Depression as Revealed in Internet Blogs*. Soical Theory and Health. submitted for publication.
- Coppen, A. (1967). The biochemistry of affective disorders. *Br. J. Psychiatry*, 113(504), 1237–1264.
- Delgado, P. L. (2000). Depression: the case for a monoamine deficiency. *J. Clin. Psychiatr.*, 61(Suppl. 6), 7–11.
- Demasi, M., & Gotzsche, P. C. (2020). Presentation of benefits and harms of antidepressants on websites: a cross-sectional study. *Int. J. Risk Saf. Med.*, 31(2), 53–65.
- Dunn, A. L., & Dishman, R. K. (1991). Exercise and the neurobiology of depression. *Exerc. Sport Sci. Rev.*, 19, 41–98.
- Eske, J. (2019). Everything you need to know about chemical imbalances in the brain [Internet] *MedicalNewsToday*, 16th Nov 2021. Available from: <https://www.medicalnewstoday.com/articles/326475>.
- Eveleigh, R., Speckens, A., van Weel, C., Oude Voshaar, R., & Lucassen, P. (2019). Patients' attitudes to discontinuing not-indicated long-term antidepressant use: barriers and facilitators. *Ther. Adv. Psychopharmacol.*, 9, Article 2045125319872344.
- Fennell LB, M. (2015). *When Doctors Mislead; the Chemical Imbalance Lie*, 13th Oct 2021. Available from: <https://davidhealy.org/wp-content/uploads/2016/06/When-doctors-mislead-the-chemical-imbalance-lie.pdf>.
- Fox, D. (13th Oct 2021). *A Worldwide Epidemic – the Misuse of Anti-depressant Medications 2016*. Available from: <https://www.madinamerica.com/2016/05/a-worldwide-epidemic-the-misuse-of-anti-depressant-medications/>.
- France, C. M., Lysaker, P. H., & Robinson, R. P. (2007). The "Chemical Imbalance" explanation for depression: origins, lay endorsement, and clinical implications. *Prof. Psychol. Res. Pract.*, 411–420.
- Fullagar, S., & O'Brien, W. (2013). Problematising the neurochemical subject of antidepressant treatment: the limits of biomedical responses to women's emotional distress. *Health (London)*, 17(1), 57–74.
- Gelder, M., Andreasen, N., Lopez-Ibor, J., & Geddes, J. (2009). *The New Oxford Textbook of Psychiatry* (second ed.). Oxford: Oxford University Press. second ed.
- Graeff, F. G., Guimaraes, F. S., De Andrade, T. G., & Deakin, J. F. (1996). Role of 5-HT in stress, anxiety, and depression. *Pharmacol. Biochem. Behav.*, 54(1), 129–141.
- Harmer, C. J., & Cowen, P. J. (2018). How do drugs for psychiatric disorders work? *Epidemiol. Psychiatr. Sci.*, 27(2), 141–142.
- Healy, D. (1987). The structure of psychopharmacological revolutions. *Psychiatr. Dev.*, 5(4), 349–376.
- Healy, D. (1997). *The Antidepressant Era*. New York: Harvard University Press.
- Healy, D. (2015). Serotonin and depression. *BMJ*, 350, h1771.
- Heim, C., Owens, M. J., Plotsky, P. M., & Nemeroff, C. B. (1997). The role of early adverse life events in the aetiology of depression and posttraumatic stress disorder. Focus on corticotropin-releasing factor. *Ann. N. Y. Acad. Sci.*, 821, 194–207.
- Hickey, P. (13th Oct 2021). *More on the Chemical Imbalance Theory 2015*. Available from: <https://www.behaviorismandmentalhealth.com/2015/11/02/more-on-the-chemical-imbalance-theory/>.
- Jakobsen, J. C., Gluud, C., & Kirsch, I. (2019). Should antidepressants be used for major depressive disorder? *BMJ Evid Based Med*.
- Johnstone, E. C., Freeman, C., & Zealley, A. K. (1998). *Companion to Psychiatric Studies* (sixth ed.). Edinburgh: Harcourt Brace. sixth ed.
- Kramer, P. D. (1993). *Listening to Prozac: A Psychiatrist Explores Antidepressant Drugs and the Remaking of the Self*. New York: Viking Press.
- Krishnan, V., & Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature*, 455(7215), 894–902.
- Krishnan, V., & Nestler, E. J. (2010). Linking molecules to mood: new insight into the biology of depression. *Am. J. Psychiatr.*, 167(11), 1305–1320.
- Lacasse, J. R., & Leo, J. (2005). Serotonin and depression: a disconnect between the advertisements and the scientific literature. *PLoS Med.*, 2(12), e392.
- Licinio, J., & Wong, M. L. (1999). The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. *Mol. Psychiatr.*, 4(4), 317–327.
- Lipsman, N., & Lozano, A. M. (2011). The most cited works in major depression: the 'Citation classics'. *J. Affect. Disord.*, 134(1–3), 39–44.
- Lopez-Munoz, F., & Alamo, C. (2009). Monoaminergic neurotransmission: the history of the discovery of antidepressants from 1950s until today. *Curr. Pharmaceut. Des.*, 15(14), 1563–1586.
- Maes, M., & Meltzer, H. Y. (1995). The serotonin hypothesis of major depression. In *Psychopharmacology: the Fourth Generation of Progress* (pp. 933–944). Brentwood, TN: American College of Neuropsychopharmacology.
- Maes, M., Yirmiya, R., Noraberg, J., Brene, S., Hibbeln, J., Perini, G., et al. (2009). The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. *Metab. Brain Dis.*, 24(1), 27–53.
- Maletic, V., & Raison, C. L. (2009). Neurobiology of depression, fibromyalgia and neuropathic pain. *Front. Biosci.*, 14, 5291–5338.
- Meek, C. (2006). *SSRI Ads Questioned* (p. 754). Canadian Medical Association Journal News.
- Middlemiss, D. N., Price, G. W., & Watson, J. M. (2002). Serotonergic targets in depression. *Curr. Opin. Pharmacol.*, 2(1), 18–22.
- Middleton, N., Gunnell, D., Whitley, E., Dorling, D., & Frankel, S. (2001). Secular trends in antidepressant prescribing in the UK, 1975–1998. *J. Publ. Health Med.*, 23(4), 262–267.
- Mojtabai, R., & Olfson, M. (2010). National trends in psychotropic medication polypharmacy in office-based psychiatry. *Arch. Gen. Psychiatr.*, 67(1), 26–36.
- Moncrieff, J. (2008a). *The Myth of the Chemical Cure: a Critique of Psychiatric Drug Treatment*. Basingstoke, Hampshire, UK: Palgrave Macmillan.
- Moncrieff, J. (2008b). The creation of the concept of the antidepressant: an historical analysis. *Soc. Sci. Med.*, 66, 2346–2355.
- Moncrieff, J., & Cohen, D. (2005). Rethinking models of psychotropic drug action. *Psychother. Psychosom.*, 74(3), 145–153.
- Moncrieff JC, R.; Stockmann, T.; Amendola, S.; Hengartner, M.P.; Horowitz, M.A. The serotonin theory of depression: a systematic umbrella review of the evidence. Paper submitted to *Molecular Psychiatry*.
- Munkholm, K., Paludan-Muller, A. S., & Boesen, K. (2019). Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis. *BMJ Open*, 9(6), Article e024886.
- Nemeroff, C. B. (2002). Recent advances in the neurobiology of depression. *Psychopharmacol. Bull.*, 36(Suppl. 2), 6–23.
- Organisation for Economic Co-Operation and Development. (2020). *Statistics Health Status*. OECD [Available from: [https://stats.oecd.org/index.aspx?DataSetCode=HEALTH\\_STAT#](https://stats.oecd.org/index.aspx?DataSetCode=HEALTH_STAT#)].
- Pariante, C. M. (2018). A parallel universe where psychiatry is like the rest of medicine. *Epidemiol. Psychiatr. Sci.*, 27(2), 143–145.
- Pfizer. *Zoloft Advertisment.* (2004). USA: Burbank, California: National Broadcasting Company (NBC).
- Pies, R. W. (2011a). Psychiatry's new brain-mind and the legend of the "chemical imbalance" [Internet] *Psychiatr. Times*, 11th July 2011. Available from: <https://www.psychiatrictimes.com/view/psychiatrys-new-brain-mind-and-legend-chemical-imbalance>.
- Pies, R. W. (2011b). Doctor, is my mood disorder due to a chemical imbalance? [Internet] *Psychiatr. Times*, 12th October 2021; 12th August 2011. Available from: <https://www.psychiatrictimes.com/view/doctor-my-mood-disorder-due-chemical-imbalance>.
- Pies, R. W. (2014). Nuances, narratives, and the 'chemical imbalance' debate in psychiatry [Internet] *Medscape*, 12th October 2021. Available from: <https://openexcellence.org/nuances-narratives-chemical-imbalance-debate-psychiatry/>.
- Pies, R. W. (2015). Response to Lacasse and Leo (2015). *Behav. Therapist*, 38, 260–262.
- Pies, R. W. (2019). Debunking the two chemical imbalance myths, again [Internet] *Psychiatr. Times*, 13th Oct 2021.
- Pilkington, P. D., Reavley, N. J., & Jorm, A. F. (2013). The Australian public's beliefs about the causes of depression: associated factors and changes over 16 years. *J. Affect. Disord.*, 150(2), 356–362.



- Prins, M. A., Verhaak, P. F., Bensing, J. M., & van der Meer, K. (2008). Health beliefs and perceived need for mental health care of anxiety and depression—the patients' perspective explored. *Clin. Psychol. Rev.*, *28*(6), 1038–1058.
- Read, J., Cartwright, C., Gibson, K., Shiels, C., & Magliano, L. (2015). Beliefs of people taking antidepressants about the causes of their own depression. *J. Affect. Disord.*, *174*, 150–156.
- Read, J., Renton, J., Harrop, C., Geekie, J., & Dowrick, C. (2020). A survey of UK general practitioners about depression, antidepressants and withdrawal: implementing the 2019 Public Health England report. *Ther. Adv. Psychopharmacol.*, *10*, Article 2045125320950124.
- Ressler, K. J., & Nemeroff, C. B. (2000). Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. *Depress. Anxiety*, *12*(Suppl. 1), 2–19.
- Risch, N., Herrell, R., Lehner, T., Liang, K. Y., Eaves, L., Hoh, J., et al. (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *JAMA*, *301*(23), 2462–2471.
- Rose, N. (2004). Becoming neurochemical selves. In N. Stehr (Ed.), *Biotechnology, Commerce and Civil Society* (pp. 89–128). New Brunswick, New Jersey: Transaction Publishers.
- Royal College of Psychiatrists. (2019). *Position Statement on Antidepressants and Depression*. London: Royal College of Psychiatrists.
- Ruhe, H. G., Mason, N. S., & Schene, A. H. (2007). Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Mol. Psychiatr.*, *12*(4), 331–359.
- Sadock, B. J., Sadock, V. A., Ruiz, P., & Kaplan, H. I. (2009). *Kaplan & Sadock's Comprehensive Textbook of Psychiatry* (ninth ed.). Philadelphia, PA: Lippincott, Williams & Wilkins.
- Sahay, A., & Hen, R. (2007). Adult hippocampal neurogenesis in depression. *Nat. Neurosci.*, *10*(9), 1110–1115.
- Schildkraut, J. J. (1965). The catecholamine hypothesis of affective disorders: a review of supporting evidence. *AmJPsychiatry*, *122*(5), 509–522.
- Stahl, S. M. (1996). *Essential Psychopharmacology*. Cambridge: Cambridge University Press.
- Svenningsson, P., Chergui, K., Rachleff, I., Flajolet, M., Zhang, X., El Yacoubi, M., et al. (2006). Alterations in 5-HT1B receptor function by p11 in depression-like states. *Science*, *311*(5757), 77–80.
- Taylor, S., Annand, F., Burkinshaw, P., Greaves, F., Kelleher, M., Knight, J., et al. (2019). *Dependence and Withdrawal Associated with Some Prescribed Medicines: an Evidence Review*. London.
- Uher, R., & McGuffin, P. (2010). The moderation by the serotonin transporter gene of environmental adversity in the aetiology of depression: 2009 update. *Mol. Psychiatr.*, *15*(1), 18–22.
- Valenstein, E. (1998). *Blaming the Brain*. New York: Free Press.
- van Schaik, D. J., Klijn, A. F., van Hout, H. P., van Marwijk, H. W., Beekman, A. T., de Haan, M., et al. (2004). Patients' preferences in the treatment of depressive disorder in primary care. *Gen. Hosp. Psychiatr.*, *26*(3), 184–189.
- Wehrwein, P. (2011). Astounding increase in antidepressant use by Americans [Internet] *Harvard Health Blog*. 12th October 2021; (October 20th 2011). Available from: <https://www.health.harvard.edu/blog/astounding-increase-in-antidepressant-use-by-americans-201110203624>.
- Yu, Z., Zhang, J., Zheng, Y., & Yu, L. (2020). Trends in antidepressant use and expenditure in six major cities in China from 2013 to 2018. *Front. Psychiatr.*, *11*, 551.