# Effect of neuropsychiatric medications on mitochondrial function; for better or for worse

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Number of pages: 31
Number of words: 6466 (manuscript); 158 (abstract)
Number of figures: 3
Number of tables: 6

**Abstract**

Individuals with mitochondrial disease often present with psychopathological comorbidity, and mitochondrial dysfunction has been proposed as the underlying pathobiology in various psychiatric disorders. Several studies have suggested that medications used to treat neuropsychiatric disorders could directly influence mitochondrial function. This review provides a comprehensive overview of the effect of these medications on mitochondrial function. We collected preclinical information on six major groups of antidepressants and other neuropsychiatric medications and found that the majority of these medications either positively influenced mitochondrial function or showed mixed effects. Only amitriptyline, escitalopram, and haloperidol were identified as having exclusively adverse effects on mitochondrial function. In the absence of formal clinical trials, and until such trials are completed, the data from preclinical studies reported and discussed here could inform medication prescribing practices for individuals with psychopathology and impaired mitochondrial function in the underlying pathology.

**Keywords**: Mitochondria, Electron Transport Chain Complex Proteins, Antidepressive Agents, Drugs, in vivo studies

## Introduction

Mitochondrial involvement in complex psychopathologies has been well established (Hroudová et al., 2013; Jou et al., 2009; Karabatsiakis et al., 2014; Kato, 2007; Morava and Kozicz, 2013; Pei and Wallace, 2018; Preston et al., 2018; Rezin et al., 2009a; Rollins et al., 2009; Shao et al., 2008). Individuals with primary mitochondrial disorder due to a pathogenic variant in either the nuclear or mitochondrial genome (Rodenburg, 2011), present with a high prevalence of comorbid psychopathology compared to the general population (Anglin et al., 2012; Colasanti et al., 2020; Fattal et al., 2007; Morava et al., 2010; Rollins et al., 2009). Similarly, both genetic (primary) or acquired (secondary) mitochondrial dysfunction by, e.g. stress or toxins, has also been implicated in the pathobiology of several complex neuropsychiatric disorders including major depressive disorder (MDD) (Ferrari and Villa, 2017; Gardner and Boles, 2011; Hroudová et al., 2013; Karabatsiakis et al., 2014; Koene et al., 2009; Morava and Kozicz, 2013; Rollins et al., 2009; Wallace, 2018), anxiety disorders (Einat et al., 2005; Hovatta et al., 2010), bipolar disorder (Iwamoto et al., 2004; Konradi et al., 2004; Rollins et al., 2009; Strakowski et al., 2000), schizophrenia (Prabakaran et al., 2004; Prince et al., 1999; Rollins et al., 2009; Rollins et al., 2017), and post-traumatic stress disorder (Preston et al., 2020; Preston et al., 2018). A more causal link between mitochondrial dysfunction and depression (Gong et al., 2011; Madrigal et al., 2001; Rezin et al., 2008), anxiety (Filiou and Sandi, 2019; Hollis et al., 2015), and bipolar disorder (Andreazza et al., 2018; Bodenstein et al., 2019; Kasahara et al., 2006; Kato, 2007; Scola et al., 2013) has also been established in animal models. Interestingly, as a consequence of genetic alterations, in the case of Down syndrome, individuals may also present with secondary mitochondrial dysfunction as part of the pathobiology and often have psychopathological disturbances as a comorbidity (Vacca et al., 2019). Therefore,

78 considering the unique bioenergetic characteristics of an individual with psychiatric disease
79 should be part of clinical practice.
80 Consideration of an individual's bioenergetic status is especially important because
81 antidepressants and other neuropsychiatric medications can directly influence mitochondrial
82 function, for better or for worse, as highlighted in a recent meta-analysis for mitochondrial
83 electron transport chain (ETC) CI and CIV (Holper et al., 2019). Other reviews on this
84 subject (Adzic et al., 2016; Behr et al., 2012; de Oliveira, 2016; De Vries et al., 2020;
85 Neustadt and Pieczenik, 2008) were either not comprehensive in summarizing the
86 antidepressants' effect on all mitochondrial ETC complexes, explored other readout
87 parameters than complex activities, or investigated only a few antidepressants and their effect
88 on mitochondrial bioenergetics.
89 Several different classes of antidepressants and other neuropsychiatric medications are
90 available for the treatment of psychiatric disorders, including tricyclic antidepressants (TCAs;
91 e.g., amitriptyline, amoxapine, desipramine, imipramine, and nortriptyline), selective
92 serotonin reuptake inhibitors (SSRIs; e.g., escitalopram, fluoxetine, fluvoxamine, and
93 paroxetine), serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., desvenlafaxine,
94 duloxetine, levomilnacipran, and venlafaxine), monoamine oxidase inhibitors (MAOIs; e.g.,
95 isocarboxazid, phenelzine, selegiline), norepinephrine-dopamine reuptake inhibitors (NDRIs;
96 e.g., bupropion), and (a)typical antidepressants or antipsychotics (including agomelatine,
97 aripiprazole, clozapine, haloperidol, loxapine, olanzapine, quetiapine, risperidone, and
98 tianeptine). Other medications used to treat neuropsychiatric disorders that do not fit in any of
99 the groups mentioned above include lithium and ketamine. Bupropion is often categorized as
100 an atypical antidepressant, but here, we categorized it based on its mechanisms of action, viz.
101 the blockade of norepinephrine and dopamine reuptake (NDRI) (Ascher et al., 1995).

The absence of empirical data in humans (e.g. from formal clinical trials) combined with the prevailing anecdotal opinion that antidepressants and other neuropsychiatric medications impact mitochondrial function has led to unnecessary withholding of relevant medications from individuals with underlying primary mitochondrial disease or psychological disease with mitochondrial dysfunction in the underlying pathobiology (Hroudová et al., 2013; Jou et al., 2009; Karabatsiakis et al., 2014; Kato, 2007; Morava and Kozicz, 2013; Pei and Wallace, 2018; Preston et al., 2018; Rezin et al., 2009a; Rollins et al., 2009; Shao et al., 2008). Furthermore, guidance is often sought when prescribing antidepressants or other neuropsychiatric medications for individuals with psychopathology and comorbid mitochondrial dysfunction. Our aim is to provide a consolidated resource of preclinical evidence in order to provide a transparent, and unbiased resource on the effects of neuropsychiatric medications on mitochondrial ETC complex function and closely related enzymes.

**Methods**

PubMed was used to search for original studies published in the English language between January 1975 and August 2020, investigating the effect of antidepressants or other neuropsychiatric medications on mitochondrial function *in vivo*. The following search string was used, resulting in 785 hits: (antidepressant OR antidepressants OR "antidepressant drugs") AND (mitochondria OR "mitochondrial function" OR "mitochondrial dysfunction" OR "electron transport chain" OR "oxidative phosphorylation") AND ("*in vivo*" OR rat OR mouse OR animal). The title and abstract of these 785 hits were screened for eligibility based on the following inclusion and exclusion criteria. Additionally, the authors reviewed the references of identified papers for eligible studies missed during the initial literature search. This search resulted in the inclusion of 46 articles in the review (Fig. 1).

Inclusion criteria: 1) *In vivo* rodent studies; 2) Studies investigating antidepressants or other neuropsychiatric medications on mitochondrial ETC complex activity as a primary outcome measurement; 3) Studies using non-genetically modified animals; 4) Only naïve animals were considered since pre-treatment with other drugs or stress can also directly influence mitochondrial protein expression and function, primarily in a negative manner (Głombik et al., 2016; Głombik et al., 2018; Gong et al., 2011; Madrigal et al., 2001; Picard and McEwen, 2018; Rezin et al., 2008); 5) Articles representing a primary research paper; 6) Full text available (conference abstracts excluded).

Exclusion criteria: Studies solely reporting on protein expression, mitochondrial membrane potential, mitochondrial morphology, mitophagy, mitochondrial DNA copy number and integrity, and oxidative stress parameters. Although all these processes are linked to mitochondrial function, they are either upstream or downstream of mitochondrial ETC function, and the focus of this review is mitochondrial ETC complex activity. In addition, *in vitro* studies and studies on discontinued antidepressants have been excluded.

**Assessing mitochondrial function**

In order to assess the effects of antidepressants and other neuropsychiatric medications on mitochondrial energy metabolism, in this review we specifically focused on the mitochondrial electron transport chain (ETC) complex activity (function). The ETC is comprised of four enzymatic complexes situated in the inner mitochondrial membrane. In short, complex I through complex IV (NADH:ubiquinone oxidoreductase [CI], succinate dehydrogenase [CII or SDH], ubiquinol:cytochrome c oxidoreductase [CIII], and cytochrome C oxidase [CIV]) are part of the ETC (also called the respiratory chain) where NADH and FADH are utilized to transport electrons along the different complexes. The final electron acceptor is oxygen ($O_2$) at CIV, which is then oxidized to water ($H_20$). This transfer of

electrons generates energy which is subsequently used to pump protons over the mitochondrial inner membrane from the mitochondrial matrix to the intermembrane space establishing an electrochemical gradient. This so-called proton motive force, or membrane potential, is then harnessed by ATP synthase (complex V; CV) to produce the high energy content molecule of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and inorganic phosphate (Pi). This whole process is called oxidative phosphorylation (OXPHOS) (**Fig. 2A**).

The activity of each complex can be measured directly and individually using spectrophotometric measurement approaches (Rodenburg, 2011). Additionally, enzymes involved in the Krebs cycle, such as citrate synthase (CS) or malate dehydrogenase (MDH), can be analyzed. CS catalyzes the first step in the Krebs cycle. CS is often used as a proxy for the mitochondrial matrix, as a measure of the intactness of isolated mitochondria, or to test the matrix purity after mitochondrial subfractions. CS is also a widely used proxy in clinical practice as well as in our field of research for mitochondrial mass. MDH catalyzes the last step of the Krebs cycle and has also been related to the pathology of MDD (Scaini et al., 2010).

In addition to the activities of the individual complexes, respiration analysis is also frequently used to investigate mitochondrial function, with oxygen consumption acting as a readout parameter. State 3 and state 4 respiration in the presence of different substrates are often reported using these assays. State 3 respiration measures ADP-stimulated oxygen consumption by intact mitochondria. Conversely, state 4 respiration measures oxygen consumption in the absence of ADP, which measures the energy required for the maintenance of the membrane potential.

Lastly, four studies included in this review measured mitochondrial complex IV (CIV) activity using histochemical stainings (González-Pardo et al., 2008; Lambert et al., 1999;

177 Prince et al., 1998; Shumake et al., 2010). It is important to note that this technique gives
178 insight into CIV activity; however, the results are not interchangeable with
179 spectrophotometric CIV measurements.
180
181 **The impact of antidepressants and other neuropsychiatric medications on**
182 **mitochondrial function**
183 In this section we focused on the effects of different antidepressants and other
184 neuropsychiatric medications on mitochondrial function. We divided them into six segments
185 according to the different drug classes and summarized those classes and their overall effects
186 on mitochondrial function. We also discussed the potential clinical relevance of these
187 findings and some suggestions for future study.
188
189 *Tricyclic antidepressants (TCAs)*
190 TCAs were among the first antidepressants developed (Stahl, 1998). Although they
191 have mostly been replaced over time by alternatives with fewer side effects, TCAs remain a
192 last resort after other antidepressants have failed. They work by blocking the reuptake of
193 serotonin and norepinephrine but also interact with several other receptor sites, including
194 histamine, acetylcholine, and epinephrine receptors (Feighner, 1999; Stahl, 1998). The
195 interaction with these other receptor sites predominantly causes the adverse side effects of
196 TCAs (Feighner, 1999). There are currently several licensed TCAs on the market. Impact on
197 mitochondrial function has only been assessed for four of the TCAs: amitriptyline,
198 desipramine, imipramine, and nortriptyline. Results are summarized in **Table 1**.
199 We identified one study investigating amitriptyline and its effect on the complexes of
200 the mitochondrial ETC. The authors found that a single intraperitoneal (ip) administration of

amitriptyline negatively influenced complex IV (CIV) activity in several different brain areas of male CD1 mice (González-Pardo et al., 2008), an outbred mouse strain.

This negative effect of amitriptyline contrasts with studies investigating desipramine (Villa et al., 2017; Villa et al., 2016). Specifically, the effect of chronic desipramine administration in male Sprague Dawley rats was investigated. Desipramine increased the activity of CS in both studies. Depending on the brain area, CIV activity was either increased in the frontal cortex and hippocampus (Villa et al., 2017; Villa et al., 2016) or decreased in the hippocampus (Villa et al., 2017). Complex II (CII) and MDH activities were consistently found to be decreased after desipramine treatment in both studies in the frontal cortex but not in the hippocampus (Villa et al., 2017; Villa et al., 2016). These results suggest a potential brain area-specific effect of desipramine on mitochondrial function.

The tricyclic antidepressant that was investigated in the most studies returned was imipramine, which mostly shows positive or neutral effects on mitochondrial function after acute or chronic treatments (Abelaira et al., 2011; Della et al., 2012; Katyare and Rajan, 1988; Katyare and Rajan, 1995; Réus et al., 2012a; Réus et al., 2012b). The majority of studies in male Wistar rats showed an increased CII activity after acute or chronic administration in several different brain regions (Abelaira et al., 2011; Della et al., 2012; Réus et al., 2012a; Réus et al., 2012b). Furthermore, CS increased in two studies following acute administration; however, this effect was gone following chronic administration (Abelaira et al., 2011; Della et al., 2012). Two studies using female Wistar rats showed, in general, an increase in state 3 and state 4 respiration in the brain (Katyare and Rajan, 1995) as well as the liver (Katyare and Rajan, 1988).

Besides these positive effects of imipramine, it seems mitochondrial complex I (CI) function in the prefrontal cortex was negatively affected in male Wistar rats following a single injection (Abelaira et al., 2011; Della et al., 2012). Interestingly, this finding was not

present after chronic imipramine treatment (Abelaira et al., 2011; Della et al., 2012). Réus et al. (2012a) reported increased CI activity in the striatum but decreased CI activities in the hippocampus and striatum after a single imipramine administration. In contrast, chronic imipramine treatment resulted in increased CI activity in the prefrontal cortex (Réus et al., 2012a).

Lastly, the TCA nortriptyline was investigated in two studies returned, and mainly exhibited neutral or positive effects on mitochondrial function (Scaini et al., 2011; Scaini et al., 2010). Nortriptyline increased CI, CII, and CIV activity in several brain areas following chronic administration in male Wistar rats (Scaini et al., 2010)(Scaini et al., 2011).

*Selective serotonin reuptake inhibitors (SSRIs)*

The most widely prescribed treatments for MDD and several other psychopathologies are SSRIs (Moore and Mattison, 2017; Olfson and Marcus, 2009). As the name implies, they work by selectively inhibiting serotonin reuptake by neurons. SSRIs have similar efficacy to TCAs, only with fewer side effects (Anderson, 2000; Undurraga and Baldessarini, 2017). Because of these fewer side effects, treatment discontinuation is lower relative to TCA treatments (Anderson, 2000). Currently, several different SSRIs are used to treat neuropsychiatric disorders. Our literature search identified four SSRIs (escitalopram, fluoxetine, fluvoxamine, and paroxetine) whose effect on mitochondrial function had been assessed. Results are summarized in **Table 2**.

We identified two studies investigating the effect of escitalopram on mitochondrial functioning (Gonçalves et al., 2012; Shetty et al., 2015). The first study showed that chronic escitalopram treatment in male Wistar rats resulted in an overall negative effect on mitochondrial function. More specifically, CI, CII, and complex II+III (CII-CIII) activities were all found to be decreased in several different brain regions, including the cerebellum,

hippocampus, and striatum (Gonçalves et al., 2012). Conversely, one study found no effect of chronic escitalopram treatment on mitochondrial functioning in female Wistar rats, although, in this study, only whole brain homogenate was used to investigate mitochondrial activities (Shetty et al., 2015).

The majority of the studies investigating SSRIs used fluoxetine; we identified thirteen studies investigating mitochondrial function following fluoxetine treatment (Adzic et al., 2013; Adzic et al., 2017; Agostinho et al., 2011a; Agostinho et al., 2011b; da Silva et al., 2015a; da Silva et al., 2015b; Shumake et al., 2010; Simões-Alves et al., 2018; Sonei et al., 2017; Souza et al., 1994; Tutakhail et al., 2019; Villa et al., 2017; Villa et al., 2016). Based on these studies, one cannot easily conclude whether fluoxetine has a positive or negative effect on mitochondrial function. Some studies report overall positive or neutral effects on mitochondrial function (Adzic et al., 2017; Agostinho et al., 2011a; Sonei et al., 2017; Tutakhail et al., 2019), while other studies found differing effects depending on, for example, the brain region or dose of administration (Adzic et al., 2013; Agostinho et al., 2011b; Shumake et al., 2010; Souza et al., 1994; Villa et al., 2017; Villa et al., 2016).

Despite these differences, several similar outcomes were observed between studies following fluoxetine treatment. First, it seems that after acute or chronic administration, state 4 respiration is elevated (da Silva et al., 2015a; da Silva et al., 2015b; Simões-Alves et al., 2018; Souza et al., 1994), which would indicate the mitochondria spent more energy on sustaining the membrane potential. Second, several studies reported that fluoxetine has either no effect on CS activity (Agostinho et al., 2011a; Agostinho et al., 2011b; Tutakhail et al., 2019; Villa et al., 2017) or increased CS activity following acute administration (Agostinho et al., 2011a). This increased activity could either indicate a positive effect on mitochondrial biogenesis after a single injection, which is no longer present after chronic treatment, or this

could reflect a compensatory mechanism caused by mitochondrial dysfunction or increased energy demand following the administration of fluoxetine.

Only a few studies investigated CI and CII while no studies investigated complex III (CIII) function following fluoxetine administration. The one study investigating CI activity found that acute administration increased CI activity in male Wistar rats (Agostinho et al., 2011b), while chronic administration lowers its activity (Agostinho et al., 2011b). Conversely, CII activity after chronic fluoxetine treatment was either found to be unaltered in male Wistar rats (Agostinho et al., 2011b) or decreased in male Sprague Dawley rats (Villa et al., 2016).

Most studies returned analyzed mitochondrial CIV activity following fluoxetine treatment. Acute fluoxetine administration does not seem to influence CIV activity in male Wistar rats (Agostinho et al., 2011b). Conversely, chronic treatment resulted in positive or negative effects (Adzic et al., 2013; Adzic et al., 2017; Agostinho et al., 2011b; Shumake et al., 2010; Villa et al., 2017; Villa et al., 2016). Fluoxetine's effect on CIV depended on the dose, the investigated brain area, as well as the animal model used. For example, chronic treatment of male "congenitally helpless" Sprague Dawley rats, a rat model of susceptibility to affective disorders, resulted in increased CIV activity in the ventral tegmental area (Shumake et al., 2010). At the same time, the habenula, dentate gyrus, and dorsomedial prefrontal cortex exhibited decreased CIV activity (Shumake et al., 2010), while Villa et al. (2016) found increased CIV activity in the frontal cortex after chronic fluoxetine administration in male Sprague Dawley rats (Villa et al., 2016). One study investigated the effect of fluoxetine (administered via the drinking water) on mitochondrial function in male Balbc-j mice and found no effect on mitochondrial CIV activity in the skeletal muscle (Tutakhail et al., 2019).

Interestingly, sex-specific effects following chronic fluoxetine treatment have also been reported in Wistar rats (Adzic et al., 2013; Adzic et al., 2017). Specifically, CIV activity was not altered in the hippocampus in female Wistar rats (Adzic et al., 2013; Adzic et al., 2017), while it was increased in the hippocampus and decreased in the prefrontal cortex in male Wistar rats (Adzic et al., 2013; Adzic et al., 2017).

Comparable to fluoxetine's effect on mitochondrial function, chronic fluvoxamine administration showed mixed results on bioenergetics in male Wistar rats (Ferreira et al., 2014). Fluvoxamine treatment resulted in an increased CS activity in the prefrontal cortex but decreased CS activity in the cerebellum, hippocampus, and cortex. In a similar pattern, CI was found to be decreased in the hippocampus and striatum (Ferreira et al., 2014). Interestingly 10 mg/kg fluvoxamine decreased CI activity, while 30 mg/kg increased CI activity in the prefrontal cortex, suggesting a dose-dependent effect on mitochondrial function (Ferreira et al., 2014). In summary, one can conclude that chronic fluvoxamine treatment results in diverging effects on mitochondrial complex activities in different brain regions in response to different doses. For more details, consult **Table 2**.

Paroxetine treatment seems to have positive effects on mitochondrial function in male Wistar rats (Scaini et al., 2011; Scaini et al., 2010). Chronic paroxetine administration increased CS activity, indicating an increased number of mitochondria, as well as increased CI, CII, and CIV activities in several brain areas, including the prefrontal cortex, hippocampus, and striatum (Scaini et al., 2011; Scaini et al., 2010).

*Serotonin-norepinephrine reuptake inhibitors (SNRI)*

SNRIs are mostly used as second-line treatments (Forns et al., 2019), and work as dual inhibitors of both serotonin and norepinephrine reuptake. Of the currently available SNRIs, we only identified studies assessing venlafaxine's effect on mitochondrial function

(Scaini et al., 2011; Scaini et al., 2010). These findings are summarized in **Table 3**. Venlafaxine increased CII and CIV activity in the prefrontal cortex, and CII activity in the hippocampus and striatum of male Wistar rats following chronic administration (Scaini et al., 2011; Scaini et al., 2010).

*Norepinephrine-dopamine reuptake inhibitors (NDRI)*

NDRIs do not directly influence the serotonin system; they work by inhibiting the reuptake of norepinephrine and dopamine. In the class of NDRIs, only bupropion is used to treat depression (Stahl, 1998), and we only identified one study investigating its effect on mitochondrial function (Ferreira et al., 2012). The results are summarized in **Table 4**. The authors' main observation was that chronic treatment with bupropion increased CII activity in several brain regions, including the hippocampus, striatum, prefrontal cortex, and cerebellum in male Wistar rats (Ferreira et al., 2012). The authors did not report any effect on other complexes of the ETC (Ferreira et al., 2012).

*(A)typical antipsychotics*

Antipsychotics are primarily used to treat hallucinations and delusions in patients with neuropsychiatric disorders, while one of the most common off-label uses of antipsychotics is for treatment-resistant depression (Meltzer, 2013). There are two main classes of antipsychotics; typical and atypical antipsychotics, with typical antipsychotics being dopamine antagonists, and atypical antipsychotics being dopamine and serotonin antagonists (Stahl, 2013). Several mechanisms might explain the working mechanism for antipsychotics as antidepressants. These include the blockade of neurotransmitter receptors and monoamine transporters, effects on sleep, decrease of cortisol levels, and an increase in neurotrophic growth factors (Sagud et al., 2011). Of the several available typical antipsychotics, only

haloperidol was included in this review. Several more atypical antipsychotics were included, including aripiprazole, clozapine, and olanzapine. The results are summarized in **Table 5**.

Only one report investigating the effect of aripiprazole on mitochondrial function was identified (Streck et al., 2007). After chronic administration, Streck et al. (2007) reported increased CII activity in the prefrontal cortex at the highest administered concentration in male Wistar rats, whereas no effect on CIV was found (Streck et al., 2007).

Of the three studies we identified which investigated clozapine (Prince et al., 1997, 1998; Streck et al., 2007), two observed an increase in CIV activity in several brain areas, including the frontal cortex and hippocampus of male Sprague Dawley rats chronic (Prince et al., 1997, 1998). Conversely, Streck et al. (2007) found no effect on CIV activity but reported a decreased CII activity in the striatum of male Wistar rats following chronic clozapine (Streck et al., 2007).

The same three studies that investigated clozapine also investigated the effects of haloperidol on mitochondrial function (Prince et al., 1997, 1998; Streck et al., 2007). Independent of duration (acute or chronic), CI activity was decreased in several brain areas of male Sprague Dawley rats following haloperidol administration (Prince et al., 1997, 1998). In contrast, haloperidol exhibited a time-dependent effect on CIV activity in the frontal cortex, After a short administration, no effect was measured, while after chronic administration for 14 days, CIV activity was decreased. However, following a more prolonged administration of 28 days, CIV activity increased (Prince et al., 1997). This increase in the frontal cortex after 28 days was confirmed in a follow-up study. Interestingly, the same study found that 28 days of haloperidol administration resulted in decreased CIV activity in the cerebellum (Prince et al., 1998). In male Wistar rats, no effect of haloperidol was found on CIV in several brain areas, but CII activity was decreased in the hippocampus and striatum of chronically treated male Wistar rats (Streck et al., 2007).

Three studies returned investigated olanzapine's effects on mitochondrial function (Agostinho et al., 2011a; Agostinho et al., 2011b; Streck et al., 2007). A single injection of olanzapine increased CI, CII, and CS activity in the prefrontal cortex, striatum, and hippocampus of male Wistar rats, but decreased CIV activity in the hippocampus (Agostinho et al., 2011a; Agostinho et al., 2011b). Chronic treatment, however, decreased CII activity in the cerebellum, and CIV activity in the hippocampus, while increasing the CII-CIII activity in the striatum (Agostinho et al., 2011b; Streck et al., 2007).

*Other drugs*

The remaining drugs that do not fit into a specific antidepressant category, but can be used for the treatment of depression, are shown in **Table 6**. In total, twenty studies were identified investigating eight different drugs: agomelatine, harmine, ketamine, lithium, memantine, methylphenidate, tianeptine, and valproate. The relatively novel atypical antidepressant agomelatine is a melatonergic $MT_1$ and $MT_2$ receptor agonist and serotoninergic 5-$HT_{2b}$ and 5-$HT_{2c}$ receptors antagonist (Guaiana et al., 2013). Harmine is a β-carboline that produces antidepressant-like effects in animal experiments (Liu et al., 2017). Ketamine and memantine are both glutamate N-methyl-D-aspartate (NMDA) receptor antagonists (Abdallah et al., 2015; DeWilde et al., 2015) with antidepressant effects (Ates-Alagoz and Adejare, 2013). Ketamine is classically used as an anaesthetic (Kurdi et al., 2014), but in recent years subanesthetic doses of ketamine have shown promise as a treatment for depression; it is mostly known for its rapid effects in patients with treatment-resistant depression (Serafini et al., 2014). Memantine is typically used in treating Alzheimer disease, but an increasing number of studies have investigated its antidepressant effects (Zdanys and Tampi, 2008). Lithium is mainly used as a mood-stabilizing agent that can also be used as an adjunctive treatment for MDD or in individuals suffering from treatment-resistant depression

399 (Edwards et al., 2013). Methylphenidate is usually prescribed to treat attention deficit
400 hyperactivity disorder (Challman and Lipsky, 2000). While the mode of action of
401 methylphenidate is similar to that of NDRIs, we have categorized it here as, in clinical
402 practice, it is rarely categorized as an NDRI, regardless of its mechanism of action. The
403 atypical antidepressant tianeptine increases serotonin uptake in the brain and is a μ-opioid
404 receptor agonist that can be used to treat depressive disorders, including in individuals with
405 concomitant depression and anxiety symptoms (Gassaway et al., 2014; Kasper and McEwen,
406 2008; Wagstaff et al., 2001). Valproate is mainly used to treat bipolar disorders (Citrome,
407 2014; Liu, 2014), but has recently also been found to be an effective adjunctive treatment in
408 individuals with treatment-resistant depression (Fengpei, 2018; Ghabrash et al., 2016).
409 We identified two studies that investigated the effect of the atypical antidepressant
410 agomelatine on mitochondrial function (de Mello et al., 2016; Gupta and Sharma, 2014). The
411 first did not find any effect of agomelatine on mitochondrial function in either male or female
412 Wistar rats after chronic administration (Gupta and Sharma, 2014). The second study, on the
413 other hand, found several mixed effects of agomelatine on mitochondrial function (de Mello
414 et al., 2016). After chronic administration of lower doses, agomelatine increased, but at
415 higher doses decreased CI activity in the prefrontal cortex, cerebellum, and striatum of male
416 Wistar rats (de Mello et al., 2016). For CIV activity, this phenomenon was reversed; at lower
417 concentrations agomelatine decreased, while at higher concentrations, it increased CIV
418 activity (de Mello et al., 2016). This discrepancy between studies could be attributed to the
419 differential experimental setups: Gupta and Sharma (2014) gave the drug via an oral cannula
420 with lower doses compared to the study by de Mello et al. (2016), which utilized higher-dose
421 ip injections.
422 One study returned investigating harmine demonstrated that a single dose increased
423 CI and CIV activity in the striatum in male Wistar rats (Réus et al., 2012a). Chronic

administration of harmine gave similar effects on mitochondrial function as a single administration (Réus et al., 2012a).

Ketamine and its effect on mitochondrial function was investigated in five studies, all using male Wistar rats (Rezin et al., 2010; Rezin et al., 2009b; Venâncio et al., 2013; Venâncio et al., 2015; Zugno et al., 2015). The results from these studies are relatively heterogeneous with two studies reporting no effect on mitochondrial activity after either a single injection (Rezin et al., 2009b) or chronic administration of ketamine (Rezin et al., 2010). Another study reported both positive, as well as negative effects, depending on the brain area and the investigated mitochondrial ETC complex after a single ketamine injection (Zugno et al., 2015). In addition to the brain, mitochondrial activity was also investigated in the rat liver following chronic ketamine administration (Venâncio et al., 2013). This prolonged administration resulted in a decreased CI activity, as well as increased state 3 and state 4 respiration rates in the presence of the substrates glutamate and malate (Venâncio et al., 2013). In addition, Venâncio et al. (2015) investigated ketamine administration at higher concentrations (50-150 mg/kg ip injections) compared to the aforementioned studies (Rezin et al., 2010; Rezin et al., 2009b; Venâncio et al., 2013; Zugno et al., 2015) which primarily resulted in an increased state 4 respiration and decreased CI activity in the brain following a single injection (Venâncio et al., 2015).

Seven studies returned investigated the effects of lithium on mitochondrial activity (Bachmann et al., 2009; Feier et al., 2013; Kim et al., 2016; Lambert et al., 1999; Streck et al., 2015; Tan et al., 2012; Valvassori et al., 2010). In general, most studies returned concluded that lithium did not affect mitochondrial function, based on multiple animal models, administration durations, administration methods, as well as multiple brain areas investigated (Bachmann et al., 2009; Feier et al., 2013; Kim et al., 2016; Lambert et al., 1999; Streck et al., 2015; Tan et al., 2012; Valvassori et al., 2010).

We identified one study investigating the effects of memantine on mitochondrial function in male Wistar rats (Réus et al., 2012b). The activities of CI, CII, and CII-CIII were increased in the hippocampus and striatum following a single injection (though only at the lowest concentration) (Réus et al., 2012b). After chronic administration, the activities of CI (prefrontal cortex), CII (prefrontal cortex and striatum), CII-CIII (prefrontal cortex, hippocampus, striatum), and CIV (prefrontal cortex, hippocampus, striatum) were increased, while CI activity was decreased in the hippocampus and striatum (Réus et al., 2012b).

We identified two studies which investigated the effects of methylphenidate on mitochondrial function (Fagundes et al., 2010; Fagundes et al., 2007). Following a single injection, a decreased CI activity was reported in the cerebellum and prefrontal cortex of male Wistar rats (Fagundes et al., 2010). However, this decreased CI activity was not detectable following chronic administration with methylphenidate (Fagundes et al., 2010), and the activities of CII and CIV were instead increased in several brain regions, including the cerebellum, cortex, striatum, hippocampus, and prefrontal cortex (Fagundes et al., 2007).

The atypical antidepressant tianeptine and its effects on mitochondrial function was investigated by two studies (Della et al., 2012; Della et al., 2013). These studies also showed that there were differing effects of either a single or chronic administration of tianeptine on mitochondrial function in male Wistar rats. Specifically, a single injection of tianeptine decreased CS activity in the prefrontal cortex, while CS activity increased in the hippocampus following chronic administration (Della et al., 2012; Della et al., 2013). Similarly, after a single injection, CIV was not affected, while after prolonged administration, CIV activity was increased in the hippocampus (Della et al., 2012; Della et al., 2013). One finding that is consistent between acute and chronic administration of tianeptine is the increased activity of CII-CIII in the hippocampus (Della et al., 2012; Della et al., 2013).

Lastly, we identified four studies that met our inclusion criteria analyzing the effects of valproate on mitochondrial function (Bachmann et al., 2009; Feier et al., 2013; Streck et al., 2015; Valvassori et al., 2010). Similar to the lithium treatment studies, most mitochondrial parameters were not affected by administration of valproate (Bachmann et al., 2009; Feier et al., 2013; Streck et al., 2015; Valvassori et al., 2010). However, one study showed positive effects following valproate administration, namely an increased CII activity in the cerebral cortex of C57BL/6 mice (Streck et al., 2015). It is important to note that the specific C57BL/6 strain cannot be determined based on the information provided. This would have been important information since there are several C57BL/6 mouse strains. The C57BL/6J and C57BL/6Jcrl strains lack an important mitochondrial enzyme caused by a deletion in the nicotinamide nucleotide transhydrogenase (Nnt) gene, while two other strains possess this gene (C57BL/6N and C57BL/6eiJ). A lack of NNT could have direct effects on mitochondrial function, making it important to specify and be considered when interpreting findings from different C57BL/6 mouse strains (Bertero and Maack, 2018; Enríquez, 2019; Ho et al., 2017).

## Discussion

Antidepressants are the first line of treatment in various psychiatric diseases. The complex and heterogeneous nature of most psychiatric diseases results in differing treatment response. Specifically, only about 50% of individuals experience remission and a relatively large percentage of individuals do not respond, or develop resistance, to antidepressant medications (Al-Harbi, 2012; Kessler et al., 2003). Therefore, identifying modulators of treatment response and personalized treatment are of utmost relevance. One such modulator could be mitochondrial dysfunction (also see introduction). Therefore, considering the unique bioenergetic characteristics of an individual with psychological disease could lead to

personalized antidepressant treatment suited to their underlying mitochondrial bioenergetic capacity, in a personalized medicine approach.

We highlighted antidepressants and other neuropsychiatric medications from several different classes and their effects on mitochondrial function. We found that several of these medications positively influenced mitochondrial function, including nortriptyline, paroxetine, venlafaxine, bupropion, aripiprazole, and memantine (**Fig. 2B**). Several other medications showed both positive and negative influences on mitochondrial function, including imipramine, desipramine, fluoxetine, fluvoxamine, methylphenidate, agomelatine, clozapine, olanzapine, tianeptine, ketamine, and lithium (**Fig. 2B**). Ultimately the effects of antidepressants and other neuropsychiatric medications on mitochondrial function appear to depend on the particular brain area, the treatment duration, and the concentration of the drug administered. Lastly, we also identified three drugs that had detrimental effects on mitochondrial function, including amitriptyline, escitalopram, and haloperidol (**Fig. 2B**). Interestingly, the effects of the antidepressants and other neuropsychiatric medications assessed in this review on mitochondrial function does not seem to relate in any way to the class of the drug. Therefore, in clinical practice, the class of antidepressant would not guide clinicians on the effect of an antidepressant on mitochondrial function.

**Limitations of the literature**

Although the effects of various antidepressants and neuropsychiatric medications on mitochondrial function in rodents is widely studied, there are still several research gaps in the field. For example, as far as we were able to ascertain, no studies investigated the effect of monoamine oxidase inhibitors on mitochondrial function.

We found several studies where not all mitochondrial complexes of the ETC were assayed. This lack of data could be important as it can mask negative or positive effects of

523 certain drugs on mitochondrial function. For example, a potentially positive effect on CIV
524 does not necessarily mean a positive effect on CI or CII as seen in, *e.g.:* (Abelaira et al.,
525 2011; Agostinho et al., 2011b; Réus et al., 2012b; Villa et al., 2016). Another limitation is
526 that we often lack confirmation of the described effects of antidepressants or other
527 neuropsychiatric medications on mitochondrial function by other laboratories/research
528 groups. Several studies presented in this review had been performed by a single laboratory
529 and have not been replicated independently by other laboratories.
530 In addition to this, none of the identified studies used CS or any other marker for
531 mitochondrial mass such as mtDNA copy number or any other specific mitochondrial
532 markers as a normalization method, instead all studies normalized to total cellular protein
533 content. Besides that, of the 45 included studies, only fifteen investigated CS activity.
534 Interestingly, approximately half of the CS results showed an increased activity following
535 administration of the several drugs investigated, highlighting the need to measure CS more
536 often. This finding is important as we already noted that CS is also a marker for
537 mitochondrial mass, indicating that these drugs may positively influence mitochondrial
538 biogenesis. This would consequently increase the total ETC complex activities, without
539 directly influencing individual ETC enzyme activities. As such, the apparent increases in
540 mitochondrial ETC complex activity observed in these studies may reflect an increase in
541 mitochondrial biogenesis and mitochondrial mass rather than a specific effect on the
542 investigated mitochondrial ETC complexes. Future research is warranted to investigate if this
543 specific increase in CS activity is a result of increased mitochondrial proliferation or another
544 mechanism. Therefore, it is important for future studies to not only normalize to total cellular
545 protein content, but also to include other measurements for normalization purposes, such as
546 citrate synthase.

Another significant limitation of the field is that there are almost no human data available (absence of formal clinical trials) on the impact of antidepressants or other neuropsychiatric medications on mitochondrial function. This limitation is mostly due to the lack of clinically validated and specific non-invasive tests to assess mitochondrial function in humans. This is important as brain bioenergetics following treatment could differ between rodents and humans. One striking example of this is the contrasting observation of valproate on mitochondrial function in humans and rodents. In rodents, several studies showed a neutral or positive effect of valproate on mitochondrial function. However, in clinical practice, it is widely agreed that valproate should only be used in exceptional circumstances in patients with mitochondrial disease because of its potentially lethal side effects, in particular in individuals with POLG disease (De Vries et al., 2020). Such critical species differences could also be the case with other medications and could hamper the translation and extrapolation of preclinical results to clinical practice and guidance on prescribing antidepressants or other neuropsychiatric medications.

Furthermore, sex differences between antidepressants and other neuropsychiatric medications and mitochondrial function have only been sparsely investigated. More specifically, only five studies returned by our criteria reported on female animals. Investigation of sex differences is necessary as clear sex biases have been reported in various psychopathologies (Karg et al., 2014; Kessler et al., 1994) and the mitochondrial physiology and mitochondrial function may likewise differ between men and women (Demarest and McCarthy, 2015; Ventura-Clapier et al., 2017).

Lastly, for the vast majority of existing licensed medications to treat neuropsychiatric disorders, mitochondrial toxicity is unknown. Therefore, it will be necessary to screen for mitochondrial toxicity in antidepressants and other neuropsychiatric medications. Given the different symptoms of depressive disorder, we would also advise the design of future clinical

studies to explore which drugs (or combination or drugs) would be advisable for a particular symptom in major depression. This would lead to more personalized treatment which would more closely respond to the need(s) of the patient.

Considering these research gaps, as well as the high importance of these data for the clinical practice, future studies including humans, sex differences, and between laboratory validations of findings are warranted before firm conclusions can be drawn.

## Conclusion

All medications that have been studied *in vivo* are summarized in **Fig. 3**. Antidepressants and other neuropsychiatric medications that are considered safe for individuals with underlying mitochondrial dysfunction are listed under the "Increase" header, drugs that require some caution are listed under the "Mixed" header, while drugs exhibiting deleterious effects on mitochondrial ETC complex activities, and which therefore should be used with caution in clinical practice, are listed under the "Decrease" header. In this context, increase and decrease refer to the effect of the drug on mitochondrial function, whereas mixed shows both increased and decreased mitochondrial function.

Despite the paucity of empirical data in humans and the absence of formal clinical trials, this review provides a transparent and unbiased opinion on antidepressants and other neuropsychiatric medications that potentially worsen mitochondrial function. Our review could guide clinical care and support a position of more conservative use of those medications treating individuals with mitochondrial disease, but also to prevent unnecessary withholding of relevant treatments from individuals with underlying primary mitochondrial disease or psychological disease with mitochondrial dysfunction in the underlying pathobiology. In the absence of formal clinical trials, and until such trials are completed, real-world data on the experience of prescribing medications to individuals with primary

mitochondrial disease should be collated and published, to further inform prescribing practice in this group of patients with complex symptomatology.

Our ability to stratify individuals with psychopathology based on their trait or acquired body/brain bioenergetics would significantly improve efforts to personalize treatment considering the unique bioenergetic characteristics of individuals with psychiatric disease. Unfortunately, currently, this is not yet possible. A potential approach could be to use more easily accessible peripheral tissues, such as blood or fibroblasts, to assess ETC complex activities, which could be used as a proxy for the bioenergetic status of the brain (Picard et al., 2018). One significant caveat is that it is highly debated how much peripheral complex activities indeed mirror brain bioenergetics, and further research is necessary to find adequate peripheral biomarkers for brain bioenergetic status. Until this becomes a reality, we recommend a more careful use of medications that negatively influence mitochondrial function for individuals with suspected primary mitochondrial disease (genetic) or secondary mitochondrial dysfunction (e.g. environmental stress, toxins *etc.*).

Notably, after a thorough review of the data, we conclude that several antidepressants or other neuropsychiatric medications could be used safely in individuals with psychopathology and comorbid mitochondrial disease or mitochondrial dysfunction while some require more caution. Only three drugs assessed (amitriptyline, escitalopram, and haloperidol) were found to have negative effects on mitochondrial function.

We recommend that combined clinical guidance of psychiatrists and clinical metabolic experts be considered when prescribing medications to individuals with psychiatric disease with mitochondrial dysfunction in the underlying pathobiology to ensure that treatment is tailored to the individual needs of the patient.

## Declaration of interest statement

Declarations of interest: none.


## Funding

T.K. and E.M. are supported by the generosity of the Marriott family. A.C.A. is supported by the Mitochondrial Innovation Initiative, MITO2i. S.R. receives grant funding from the National Institute of Health Research Great Ormond Street Hospital Biomedical Research Centre.


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990

991 **Figure legends**

992

993 **Figure 1.** Flowchart of the literature search and study selection process. n = number of
994 publications

995

996 **Figure 2**. Schematic overview of the electron transport chain (ETC) and oxidative
997 phosphorylation (OXPHOS) system and the global effect of different drugs on each measured
998 complex. **A**) As a first step, complex I (CI) and complex II (CII) oxidize NADH and FADH2.
999 The electrons generated during that process are transported through coenzyme Q (CoQ),
1000 complex III (CIII), cytochrome C (Cyt. C), and complex IV (CIV) to finally molecular
1001 oxygen. During this process, protons are pumped over the inner mitochondrial membrane to
1002 the intermembrane space by CI, CIII, and CIV, generating an electrochemical gradient. This
1003 gradient is subsequently used by complex V (CV) to generate ATP from ADP. **B**) Overview
1004 of the global effect of all investigated drugs and their effect on each complex of the ETC,
1005 state 3 and state 4 respiration, CS activity, MDH activity, as investigated by the various
1006 studies. A green '+' sign indicates an overall increased function of that specific complex
1007 following administration of that drug, a red '-' sign indicates a decreased function following
1008 administration of that drug, a yellow '/' indicates that both increased and decreased functions
1009 have been observed following administration of that drug, a dark grey '~' indicates that this
1010 complex was analyzed but there was no effect observed, whereas a light grey 'o' indicates
1011 that that specific complex is not analyzed for that drug. **References**: 1 = (Scaini et al., 2010);
1012 2 = (Scaini et al., 2011); 3 = (Ferreira et al., 2012); 4 = (Réus et al., 2012a); 5 = (Streck et al.,
1013 2007); 6 = (Bachmann et al., 2009); 7 = (Valvassori et al., 2010); 8 = (Feier et al., 2013); 9 =
1014 (Streck et al., 2015); 10 = (Katyare and Rajan, 1995); 11 = (Abelaira et al., 2011); 12 = (Réus
1015 et al., 2012b); 13 = (Della et al., 2012); 14 = (Katyare and Rajan, 1988); 15 = (Della et al.,

2013); 16 = (Fagundes et al., 2007); 17 = (Fagundes et al., 2010); 18 = (Gupta and Sharma, 2014); 19 = (de Mello et al., 2016); 20 = (Agostinho et al., 2011b); 21 = (Agostinho et al., 2011a); 22 = (Prince et al., 1997); 23 = (Prince et al., 1998); 24 = (Lambert et al., 1999); 25 = (Tan et al., 2012); 26 = (Kim et al., 2016); 27 = (Ferreira et al., 2014); 28 = (Rezin et al., 2009); 29 = (Rezin et al., 2010); 30 = (Venâncio et al., 2013); 31 = (Venâncio et al., 2015); 32 = (Zugno et al., 2015); 33 = (Souza et al., 1994); 34 = (Shumake et al., 2010); 35 = (Adzic et al., 2013); 36 = (da Silva et al., 2015a); 37 = (da Silva et al., 2015b); 38 = (Sonei et al., 2017); 39 = (Villa et al., 2016); 40 = (Adzic et al., 2017); 41 = (Villa et al., 2017); 42 = (Tutakhail et al., 2019); 43 = (Simões-Alves et al., 2018); 44 = (González-Pardo et al., 2008); 45 = (Gonçalves et al., 2012); 46 = (Shetty et al., 2015).

**Figure 3.** Summary of all antidepressants, antipsychotics, and other medications used as adjuvants for treating depression, studied concerning mitochondrial function. The different drugs are categorized based on their impact on mitochondrial function, which is either positive, mixed, or negative.

**Table legends**

**Table 1**. Summary of studies investigating the effect of different tricyclic antidepressants (TCAs) in association with mitochondrial functioning. Acute treatment is defined as a one-time administration, whereas chronic treatment durations are defined in the table. IP injections were daily in chronic administration studies unless stated otherwise.

**Table 2**. Summary of studies investigating the effect of different selective serotonin reuptake inhibitors (SSRIs) in association with mitochondrial functioning. Acute treatment is defined as a one-time administration, whereas chronic treatment durations are defined in the table. IP and subcutaneous injections were daily in chronic administration studies unless stated otherwise.

**Table 3**. Summary of studies investigating the effect of different serotonin-norepinephrine reuptake inhibitors (SNRIs) in association with mitochondrial functioning. Acute treatment is defined as a one-time administration, whereas chronic treatment durations are defined in the table. IP injections were daily in chronic administration studies unless stated otherwise.

**Table 4**. Summary of studies investigating the effect of different norepinephrine-dopamine reuptake inhibitors (NDRI) in association with mitochondrial functioning. Acute treatment is defined as a one-time administration, whereas chronic treatment durations are defined in the table. IP injections were daily in chronic administration studies unless stated otherwise.

**Table 5**. Summary of studies investigating the effect of different (a)typical antipsychotics in association with mitochondrial functioning. Acute treatment is defined as a one-time

administration, whereas chronic treatment durations are defined in the table. IP injections were daily in chronic administration studies unless stated otherwise.

**Table 6**. Summary of studies investigating the effect of different other drugs in association with mitochondrial functioning. Acute treatment is defined as a one-time administration, whereas chronic treatment durations are defined in the table. IP and subcutaneous injections were daily in chronic administration studies unless stated otherwise.

| Reference | Species studied | Dose (administration) | Brain regions/Tissue | Treatment duration (days) | Findings |
|---|---|---|---|---|---|
| **Amitriptyline** | | | | | |
| Gonzalez-Pardo et al. (2008) | Male CD1 mice<br>42 days old | 20 mg/kg<br>(ip injection) | CIV staining, multiple brain areas | Acute | CIV decreased (thalamus, anteromedial nucleus, medial septum, nucleus accumbens, nucleus basalis of Meynert, bed nucleus of the stria terminalis, diagonal band of Broca, hippocampus; CA3 subfield, hippocampus; dentate gyrus) |
| **Desipramine** | | | | | |
| Villa et al. (2016) | Male Sprague Dawley rats<br>7 weeks old | 15 mg/kg<br>(ip injection) | Frontal cortex (different mitochondrial fractions) | Chronic (21d) | CS increased (HM)<br>CII decreased (LM)<br>CIV increased (FM, HM)<br>MDH decreased (LM) |
| Villa et al. (2017) | Male CD Sprague Dawley rats<br>7 weeks old | 15 mg/kg<br>(ip injection) | Hippocampus<br>Frontal cortex (different mitochondrial fractions) | Chronic (21d) | CS increased (HM in cortex)<br>CII decreased (LM in cortex)<br>CIV increased (FM in cortex and hippocampus; HM in cortex)<br>CIV decreased (HM in hippocampus)<br>MDH decreased (LM in cortex) |
| **Imipramine** | | | | | |
| Katyare and Rajan (1988) | Female Wistar rats<br>270g | 10 mg/kg<br>(ip injection, twice daily) | Liver | Chronic (7d) | State 3 respiration increased with glutamate, beta-hydroxybutyrate, pyruvate+malate as substrates<br>State 4 respiration similar increase to state 3 respiration |
| | | | | Chronic (14d) | Similar pattern as after 7 days treatment |
| Katyare and Rajan (1995) | Female Wistar rats<br>275g | 10 mg/kg<br>(ip injection, twice daily) | Whole brain | Chronic (7d) | State 3 respiration increased with glutamate, beta-hydroxybutyrate, pyruvate+malate, and succinate as substrates - With ascorbate + TMPD state 3 decreased<br>State 4 respiration similar pattern to state 3 respiration |
| | | | | Chronic (14d) | Similar pattern as after 7 days treatment, only state 4 + succinate not significant |

| | | | | | |
|---|---|---|---|---|---|
| Abelaira et al. (2011) | Male Wistar rats 60 days old | 30 mg/kg (ip injection) | Amygdala<br>Hippocampus<br>Prefrontal cortex | Acute | CS increased (amygdala)<br>CI decreased (prefrontal cortex)<br>CII increased (amygdala)<br>CII-CIII no effect measured<br>CIV increased (hippocampus) |
| | | | | Chronic (14d) | CS no effect measured<br>CI no effect measured<br>CII increased (prefrontal cortex and hippocampus)<br>CII-III increased (prefrontal cortex, amygdala, and hippocampus)<br>CIV no effect measured |
| Della et al. (2012) | Male Wistar rats 60 days old | 30 mg/kg (ip injection) | Amygdala<br>Hippocampus<br>Nucleus accumbens<br>Prefrontal cortex | Acute | CS increased (amygdala)<br>CI decreased (prefrontal cortex)<br>CII increased (amygdala)<br>CII-III no effect measured<br>CIV no effect measured<br>MDH no effect measured |
| | | | | Chronic (14d) | CS no effect measured<br>CI no effect measured<br>CII increased (prefrontal cortex, hippocampus)<br>CII-CIII increased (prefrontal cortex, hippocampus, amygdala)<br>CIV no effect measured<br>MDH no effect measured |
| Reus et al. (2012a) | Male Wistar rats 60 days old | 10, 20, and 30 mg/kg (ip injection) | Prefrontal cortex<br>Striatum | Acute | CI no effect measured<br>CII decreased (striatum 20 and 30 mg/kg)<br>CII-CIII no effect measured<br>CIV increased (striatum 30 mg/kg) |
| | | | | Chronic (14d) | CI no effect measured<br>CII increased (prefrontal cortex, 20 mg/kg)<br>CII-CIII no effect measured<br>CIV no effect measured |

| | | | | | |
|---|---|---|---|---|---|
| Reus et al. (2012b) | Male Wistar rats 60 days old | 10, 20, and 30 mg/kg (ip injection) | Hippocampus<br>Prefrontal cortex<br>Striatum | Acute | CI increased (striatum, 10 mg/kg)<br>CII increased (hippocampus, 30 mg/kg; striatum 10 mg/kg)<br>CII-CIII no effect measured<br>CIV no effect measured |
| | | | | Chronic (14d) | CI increased (prefrontal cortex, 10 mg/kg)<br>CI decreased (hippocampus, 20 and 30 mg/kg; striatum, 30mg/kg)<br>CII increased (hippocampus, 30 mg/kg)<br>CII-CIII no effect measured<br>CIV increased (hippocampus and striatum, 30 mg/kg) |
| **Nortriptyline** | | | | | |
| Scaini et al. (2010) | Male Wistar rats 250-300g | 15 mg/kg (ip injection) | Cerebellum<br>Cortex<br>Hippocampus<br>Prefrontal cortex<br>Striatum | Chronic (15d) | CS no effect measured<br>CI increased (prefrontal cortex, hippocampus, striatum, cortex) |
| Scaini et al. (2011) | Male Wistar rats 250-300g | 15 mg/kg (ip injection) | Cerebellum<br>Cortex<br>Hippocampus<br>Prefrontal cortex<br>Striatum | Chronic (15d) | CI no effect measured<br>CII increased (hippocampus, striatum)<br>CII-III no effect measured<br>CIV increased (prefrontal cortex, striatum, cortex) |

CI = mitochondrial complex I; CII = mitochondrial complex II; CIII = mitochondrial complex III; CIV = mitochondrial complex IV; CS = citrate synthase; FM = non-synaptic mitochondria (post-synaptic); HM = intrasynaptic heavy mitochondria (presynaptic); ip = intraperitoneal; LM = intrasynaptic light mitochondria (presynaptic); MDH = malate dehydrogenase.

| Reference | Species studied | Dose (administration) | Brain regions/Tissue | Treatment duration | Findings |
|---|---|---|---|---|---|
| **Escitalopram** | | | | | |
| Goncalves et al. (2012) | Male Wistar rats<br>250-300g | 10 mg/kg<br>(ip injection) | Cerebellum<br>Hippocampus<br>Posterior cortex<br>Prefrontal cortex<br>Striatum | Chronic (14d) | CS no effect measured<br>CI decreased (cerebellum, hippocampus, striatum)<br>CII decreased (striatum)<br>CII-CIII decreased (cerebellum, hippocampus, striatum, posterior cortex)<br>CIV no effect measured<br>MDH no effect measured |
| Shetty et al. (2015) | Female Wistar rats<br>200-230g | 20 mg/kg<br>(oral administration) | Whole brain | Chronic (12d) | CI no effect measured<br>CII no effect measured<br>CIV no effect measured |
| **Fluoxetine** | | | | | |
| Souza et al. (1994) | Male Wistar Rats<br>250g | Acute: 20 mg/kg<br>Chronic: 10 mg/kg<br>(ip injection) | Liver | Acute | State 3 respiration no effect measured<br>State 4 respiration increased<br>RCR no effect measured<br>(with both alpha ketoglutarate and succinate)<br><br>No effect on Vmax |
| | | | | Chronic (12d) | No effect on state 3 respiration<br>Increased state 4 respiration<br>No effect on RCR<br>(with both alpha ketoglutarate and succinate)<br><br>Decreased Vmax |
| Shumake et al. (2010) | Male "congenitally helpless" rats (Sprague Dawley origin)<br>450-550g | 5 mg/kg<br>(ip injection) | CIV staining, multiple brain areas | Chronic (14d) | CIV increased (ventral tegmental area)<br>CIV reduced (habenula, dentate gyrus, dorsomedial prefrontal cortex) |
| Agostinho et al. (2011a) | Male Wistar rats<br>60 days old | 12.5 and 25 mg/kg<br>(ip injection) | Hippocampus<br>Prefrontal cortex<br>Striatum | Acute | CS increased (striatum, 25 mg/kg) |
| | | | | Chronic (28d) | CS no effect measured (after 2 and 24 hours) |

| | | | | | |
|---|---|---|---|---|---|
| Agostinho et al. (2011b) | Male Wistar rats<br>60 days old | 12 and 25 mg/kg<br>(ip injection) | Hippocampus<br>Prefrontal cortex<br>Striatum | Acute | CI increased (hippocampus, 25 mg/kg)<br>CII no effect measured<br>CII-CIII no effect measured<br>CIV no effect measured |
| | | | | Chronic (28d) | CI decreased (prefrontal cortex, 12 mg/kg (24h))<br>CII no effect measured<br>CII-CIII decreased (striatum, 25 mg/kg (24h))<br>CIV decreased (hippocampus, 12 and 25 mg/kg (24h))<br><br>No effects 2 hours after sacrificing |
| Adzic et al. (2013) | Male and female Wistar rats<br>3 months old | 5 mg/kg<br>(ip injection) | Hippocampus<br>Prefrontal cortex | Chronic (21d) | <u>Female</u><br>CIV increased (prefrontal cortex)<br><u>Male</u><br>CIV decreased (prefrontal cortex)<br>CIV increased (hippocampus) |
| da Silva et al. (2015a) | Male Wistar rats<br>24 hours old | 10 mg/kg<br>(subcutaneous injection) | Brown adipose tissue<br>(Measured at PND 60) | Chronic (21d) | Basal respiration rate (state 4) increased<br>Uncoupled respiration rate increased<br>Mitochondrial O2 consumption no effect measured |
| da Silva et al. (2015b) | Male Wistar rats<br>24 hours old | 10 mg/kg<br>(subcutaneous injection) | Hypothalamus<br>EDL muscle<br>(Measured at PND 60) | Chronic (21d) | CS increased (hypothalamus and EDL muscle)<br>Basal respiration rates (state 4) increased (hypothalamus and EDL)<br>ADP-stimulated respiration (state 3) increased (EDL)<br>Uncoupled respiration rate increased (hypothalamus and EDL) |
| Villa et al. (2016) | Male Sprague Dawley rats<br>7 weeks old | 10 mg/kg<br>(ip injection) | Frontal area of cortex<br>(different mitochondrial fractions) | Chronic (21d) | CII decreased (LM)<br>CIV increased (FM, HM)<br>MDH decreased (LM) |
| Adzic et al. (2017) | Male and female Wistar rats<br>3 months old | 5 mg/kg<br>(ip injection) | Hippocampus | Chronic (21d) | <u>Female</u><br>CIV no effect measured<br><u>Male</u><br>CIV increased |

| | | | | | |
|---|---|---|---|---|---|
| Sonei et al. (2017) | Male Wistar rats<br>28 days old | 7.5 mg/kg<br>(via drinking water) | Brain<br>Heart | Chronic (21d) | CII activity no effect measured<br>MDH activity no effect measured<br>Membrane potential no effect measured<br>ATP levels no effect measured |
| Villa et al. (2017) | Male Sprague Dawley rats<br>7 weeks old | 10 mg/kg<br>(ip injection) | Hippocampus | Chronic (21d) | CS no effect measured<br>CII decreased (LM in cortex and hippocampus)<br>CIV increased (FM cortex and hippocampus; HM in cortex)<br>CIV decreased (HM in hippocampus)<br>MDH decreased (LM in cortex)<br>MDH increased (HM in hippocampus) |
| Simões-Alves et al. (2018) | Wistar rats<br>24-hours old | 10 mg/kg<br>(subcutaneous injection) | Liver<br>(Measured at PND 60) | Chronic (21d) | Basal respiration rate increased<br>State 3 respiration increased<br>State 4 respiration increased<br>Uncoupled respiration rate increased |
| Tutakhail et al. (2019) | Male Balbc-j mice<br>21-25g | 18 mg/kg<br>(in drinking water) | Gastrocnemius Muscle | Chronic (6 weeks) | CS no effect measured<br>CIV no effect measured |
| **Fluvoxamine** | | | | | |
| Ferreira et al. (2014) | Male Wistar rats<br>250-300g | 10, 30, and 60 mg/kg<br>(ip injection) | Cerebellum<br>Hippocampus<br>Posterior cortex<br>Prefrontal cortex<br>Striatum | Chronic (14d) | CS increased (prefrontal cortex, 30 mg/kg)<br>CS decreased (cerebellum, 60 mg/kg; hippocampus, 60 mg/kg; cortex, 10 and 30 mg/kg)<br>CI decreased (prefrontal cortex, 10 mg/kg; hippocampus, 10 mg/kg; striatum, 10 mg/kg)<br>CI increased (prefrontal cortex, 30 mg/kg)<br>CII increased (prefrontal cortex, 30 mg/kg; cerebellum, 30 mg/kg; cortex, 10 mg/kg)<br>CII-CIII decreased (prefrontal cortex, 10 mg/kg; cerebellum, 30 and 60 mg/kg)<br>CIV decreased (prefrontal cortex, 10 and 30 mg/kg; hippocampus, 30 and 60 mg/kg; cortex, 60 mg/kg)<br>MDH decreased (prefrontal cortex, 10 mg/kg; striatum, 10, 30, 60 mg/kg) |

| Paroxetine | | | | | |
|---|---|---|---|---|---|
| Scaini et al. (2010) | Male Wistar rats 250-300g | 10 mg/kg (ip injection) | Cerebellum<br>Cortex<br>Hippocampus<br>Prefrontal cortex<br>Striatum | Chronic (15d) | CS increased (prefrontal cortex, hippocampus, striatum, cortex)<br>CII increased (prefrontal cortex, hippocampus, striatum, cortex) |
| Scaini et al. (2011) | Male Wistar rats 250-300g | 10 mg/kg (ip injection) | Cerebellum<br>Cortex<br>Hippocampus<br>Prefrontal cortex<br>Striatum | Chronic (15d) | CI increased (prefrontal cortex, hippocampus, striatum, cortex)<br>CII increased (hippocampus, striatum, cortex)<br>CII-CIII no effect measured<br>CIV increased (prefrontal cortex) |

CI = mitochondrial complex I; CII = mitochondrial complex II; CIII = mitochondrial complex III; CIV = mitochondrial complex IV; CS = citrate synthase; FM = non-synaptic mitochondria (post-synaptic); HM = intrasynaptic heavy mitochondria (presynaptic); ip = intraperitoneal; LM = intrasynaptic light mitochondria (presynaptic); MDH = malate dehydrogenase.

| Reference | Species studied | Dose (administration) | Brain regions/Tissue | Treatment duration | Findings |
|---|---|---|---|---|---|
| **Venlafaxine** | | | | | |
| Scaini et al. (2010) | Male Wistar rats 250-300g | 10 mg/kg (ip injection) | Cerebellum<br>Cortex<br>Hippocampus<br>Prefrontal cortex<br>Striatum | Chronic (15d) | CS no effect measured<br>CII increased (prefrontal cortex) |
| Scaini et al. (2011) | Male Wistar rats 250-300g | 10 mg/kg (ip injection) | Cerebellum<br>Cortex<br>Hippocampus<br>Prefrontal cortex<br>Striatum | Chronic (15d) | CI no effect measured<br>CII increased (hippocampus, striatum, cortex)<br>CII-CIII no effect measured<br>CIV increased (prefrontal cortex) |

CI = mitochondrial complex I; CII = mitochondrial complex II; CIII = mitochondrial complex III; CIV = mitochondrial complex IV; CS = citrate synthase; ip = intraperitoneal.

| Reference | Species studied | Dose (administration) | Brain regions/Tissue | Treatment duration | Findings |
|---|---|---|---|---|---|
| **Bupropion** | | | | | |
| Ferreira et al. (2012) | Male Wistar rats 250-300g | 10 mg/kg (ip injection) | Cerebellum<br>Hippocampus<br>Hypothalamus<br>Posterior cortex<br>Prefrontal cortex<br>Striatum | Chronic (14d) | CS no effect measured<br>CI no effect measured<br>CII increased (hippocampus and striatum)<br>CII-CIII no effect measured<br>CIV no effect measured<br>MDH no effect measured |

CI = mitochondrial complex I; CII = mitochondrial complex II; CIII = mitochondrial complex III; CIV = mitochondrial complex IV; CS = citrate synthase; ip = intraperitoneal; MDH = malate dehydrogenase.

| Reference | Species studied | Dose (administration) | Brain regions/Tissue | Treatment duration | Findings |
|---|---|---|---|---|---|
| **Aripiprazole** | | | | | |
| Streck et al. (2007) | Male Wistar rats 250-300g | 2, 10, and 20 mg/kg (ip injection) | Cerebellum Cortex Hippocampus Prefrontal Striatum | Chronic (28d) | CII increased (prefrontal cortex, 20mg/kg) CIV no effect measured |
| **Clozapine** | | | | | |
| Prince et al. (1997) | Male Sprague-Dawley rats 8 weeks old 250-300g | 20 mg/kg (ip injection) | Cerebellum Frontal cortex Hippocampus Striatum | Chronic (28d) | CI no effect measured CIV increased (frontal cortex and hippocampus) |
| Prince et al. (1998) | Male Sprague-Dawley rats 8 weeks old 350-400g | 20 mg/kg (ip injection) | CIV staining, multiple brain areas | Chronic (28d) | CIV increased (frontal cortex, lateral orbital cortex, CA2, CA3, CPu, core of nucleus accumbens, septum, pontine nucleus) |
| Streck et al. (2007) | Male Wistar rats 250-300g | 25 mg/kg (ip injection) | Cerebellum Cortex Hippocampus Prefrontal Striatum | Chronic (28d) | CII decreased (striatum) CIV no effect measured |
| **Haloperidol** | | | | | |
| Prince et al. (1997) | Male Sprague-Dawley rats 8 weeks old 250-300g | 1 mg/kg (ip injection) | Cerebellum Frontal cortex Hippocampus Striatum | Acute (2d) | CI decreased (striatum, frontal cortex, hippocampus, and cerebellum) CIV no effect measured |
| | | | | Chronic (14d) | CI decreased (striatum, frontal cortex, hippocampus, and cerebellum) CIV decreased (frontal cortex) |
| | | | | Chronic (28d) | CI decreased (striatum and frontal cortex) CIV increased (frontal cortex) |

| | | | | | |
|---|---|---|---|---|---|
| Prince et al. (1998) | Male Sprague-Dawley rats<br>8 weeks old<br>350-400g | 1 mg/kg<br>(ip injection) | CIV staining, multiple brain areas | Chronic (28d) | CIV increased (frontal cortex)<br>CIV decreased (cerebellum) |
| Streck et al. (2007) | Male Wistar rats<br>250-300g | 1.5 mg/kg<br>(ip injection) | Cerebellum<br>Cortex<br>Hippocampus<br>Prefrontal cortex<br>Striatum | Chronic (28d) | CII decreased (hippocampus, striatum)<br>CIV no effect measured |
| **Olanzapine** | | | | | |
| Streck et al. (2007) | Male Wistar rats<br>250-300g | 2.5, 5, and 10 mg/kg<br>(ip injection) | Cerebellum<br>Cortex<br>Hippocampus<br>Prefrontal<br>Striatum | Chronic (28d) | CII decreased (cerebellum, all concentrations)<br>CIV no effect measured |
| Agostinho et al. (2011a) | Male Wistar rats<br>60 days old | 3 and 6 mg/kg<br>(ip injection) | Hippocampus<br>Prefrontal cortex<br>Striatum | Acute | CS increased (prefrontal cortex, 6 mg/kg; hippocampus, 3 mg/kg; striatum, 3 and 6 mg/kg) |
| | | | | Chronic (28d) | CS no effect measured (2 or 24 hours) |
| Agostinho et al. (2011b) | Male Wistar rats<br>60 days old | 3 and 6 mg/kg<br>(ip injection) | Hippocampus<br>Prefrontal cortex<br>Striatum | Acute | CI increased (prefrontal cortex, 6 mg/kg; striatum, 6 mg/kg)<br>CII increased (prefrontal cortex, 6 mg/kg; hippocampus, 6 mg/kg)<br>CII-CIII no effect measured<br>CIV no effect measured |
| | | | | Chronic (28d) | CI no effect measured<br>CII no effect measured<br>CII-CIII increased (striatum, 3 mg/kg (2h))<br>CIV decreased (hippocampus, 3 and 6 mg/kg (24h)) |

CI = mitochondrial complex I; CII = mitochondrial complex II; CIII = mitochondrial complex III; CIV = mitochondrial complex IV; CS = citrate synthase; ip = intraperitoneal; MDH = malate dehydrogenase.

| Reference | Species studied | Dose (administration) | Brain regions/Tissue | Treatment duration | Findings |
|---|---|---|---|---|---|
| **Agomelatine** | | | | | |
| Gupta and Sharma (2014) | Male and female Wistar rats<br>3–5 months old<br>200–250g | 2 and 4 mg/kg<br>(oral canula) | Striatum | Chronic (19d) | CI no effect measured<br>CII no effect measured<br>CIV no effect measured |
| de Mello et al. (2016) | Male Wistar rats<br>250-300g | 10, 30, and 50 mg/kg<br>(ip injection) | Cerebellum<br>Hippocampus<br>Posterior cortex<br>Prefrontal cortex<br>Striatum | Chronic (14d) | CI increased (10mg/kg; prefrontal cortex, cerebellum, striatum)<br>CI decreased (30 and 50 mg/kg; prefrontal cortex, cerebellum, hippocampus, striatum, posterior cortex)<br>CII increased (50mg/kg; posterior cortex)<br>CIV decreased (10 and 30 mg/kg; striatum, posterior cortex)<br>CIV increased (50mg/kg; hippocampus) |
| **Harmine** | | | | | |
| Reus et al. (2012a) | Male Wistar rats<br>60 days old | 5, 10, and 15 mg/kg<br>(ip injection) | Prefrontal cortex<br>Striatum | Acute | CI increased (prefrontal cortex, 15 mg/kg; striatum, 10mg/kg)<br>CII no effect measured<br>CII-CIII no effect measured<br>CIV increased (striatum, 10mg/kg) |
| | | | | Chronic (14d) | CI increased (prefrontal cortex, 5 mg/kg)<br>CII no effect measured<br>CII-CIII no effect measured<br>CIV increased (striatum, 5 mg/kg) |
| **Ketamine** | | | | | |
| Rezin et al. (2009b) | Male Wistar rats<br>300g | 15 mg/kg<br>(ip injection) | Cerebellum<br>Cerebral cortex | Acute | CI no effect measured<br>CIII no effect measured<br>CIV no effect measured |
| Rezin et al. (2010) | Male Wistar rats<br>300g | 15 mg/kg<br>(**not specified**) | Cerebellum<br>Cerebral cortex | Chronic (7d) | CI no effect measured<br>CIII no effect measured<br>CIV no effect measured |

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|---|---|---|---|---|---|
| Venancio et al. (2013) | Male Wistar rats<br>90-110 days old | 5 and 10 mg/kg<br>(subcutaneous injection, twice daily) | Rat liver | Chronic (14d) | CI decreased both concentrations<br>CII no effect<br>CIII no effect<br>CIV no effect<br>CV no effect<br><br>State 3 - glutamate + malate decreased (both concentrations)<br>State 3 - succinate no effect<br>State 4 - glutamate + malate decreased (both concentrations)<br>State 4 - succinate no difference<br>RCR - glutamate + malate no effect<br>RCR - succinate no effect |
| Venancio et al. (2015) | Male Wistar rats<br>90-110 days old | 50, 100, and 150 mg/kg<br>(ip injection) | Brain | Acute | CI decreased (all concentrations)<br><br>State 3 respiration no effect measured<br>State 4 respiration increased (all concentrations)<br>State3/State 4 no effect measured<br>Membrane potential no effect measured |
| Zugno et al. (2015) | Male Wistar rats<br>60 days old | 5, 15, and 25 mg/kg<br>(ip injection) | Hippocampus<br>Prefrontal cortex<br>Striatum | Acute | CI no effect measured<br>CII increased (prefrontal cortex, all concentrations)<br>CII-CIII decreased (prefrontal cortex, 5 mg/kg)<br>CII-CIII increased (hippocampus and striatum 25 mg/kg)<br>CIV decreased (hippocampus, all concentrations)<br>MDH no effect measured |
| **Lithium** | | | | | |
| Lambert et al. (1999) | Male Sprague-Dawley rats<br>250-300g | Orally; lithium containing food | CIV staining, multiple brain areas | Chronic (5d)<br>Lithium concentration:<br>0.35 to 0.43 | CIV no effect measured |
| | | | | Chronic (21d)<br>Lithium concentration:<br>0.37 to 0.47 | CIV decreased (cingulate cortex and striatum) |

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|---|---|---|---|---|---|
| Bachmann et al. (2009) | Adult male Wistar Kyoto rats<br>200-250g | Orally lithium containing food | Frontal cortex | Chronic (21d) | CIV no effect measured |
| Valvassori et al. (2010) | Male Wistar rats<br>3-4 months old<br>220-310g | 47.5 mg/kg<br>(ip injection, twice daily) | Hippocampus<br>Prefrontal cortex<br>Striatum | Chronic (7d) | CI no effect measured<br>CII no effect measured<br>CIII no effect measured<br>CIV no effect measured |
| | | | | Chronic (14d) | CI no effect measured<br>CII no effect measured<br>CIII no effect measured<br>CIV no effect measured |
| Tan et al. (2012) | Male Sprague–Dawley rats<br>230–270g | Via food<br>0.55-+0.08 mM blood concentration | Frontal cortex | Chronic (21d) | CI no effect measured<br>CIII no effect measured |
| Feier et al. (2013) | Male Wistar rats<br>250-300g | 47.5 mg/kg<br>(ip injection, twice daily) | Amygdala<br>Hippocampus<br>Prefrontal cortex<br>Striatum | Chronic (7 d) | CS no effect measured<br>CI no effect measured<br>CII no effect measured<br>CII-CIII no effect measured<br>CIV no effect measured<br>MDH no effect measured |
| Streck et al. (2015) | Male C57BL/6 mice<br>30-35g | 47.5 mg/kg<br>(ip injection, twice daily) | Cerebellum<br>Cerebral cortex<br>Hippocampus<br>Prefrontal cortex<br>Striatum | Chronic (7d) | CS activity no effect measured<br>CI no effect measured<br>CII no effect measured<br>CII-CIII no effect measured<br>CIV no effect measured<br>MDH no effect measured |
| Kim et al. (2016) | Male Fisher CDF (F-344) rats<br>2 months old<br>200-250g | Via food, eventually 0.7mM plasma and brain levels | Frontal cortex | Chronic (42d) | CI no effect measured<br>CIII no effect measured<br>CV no effect measured |

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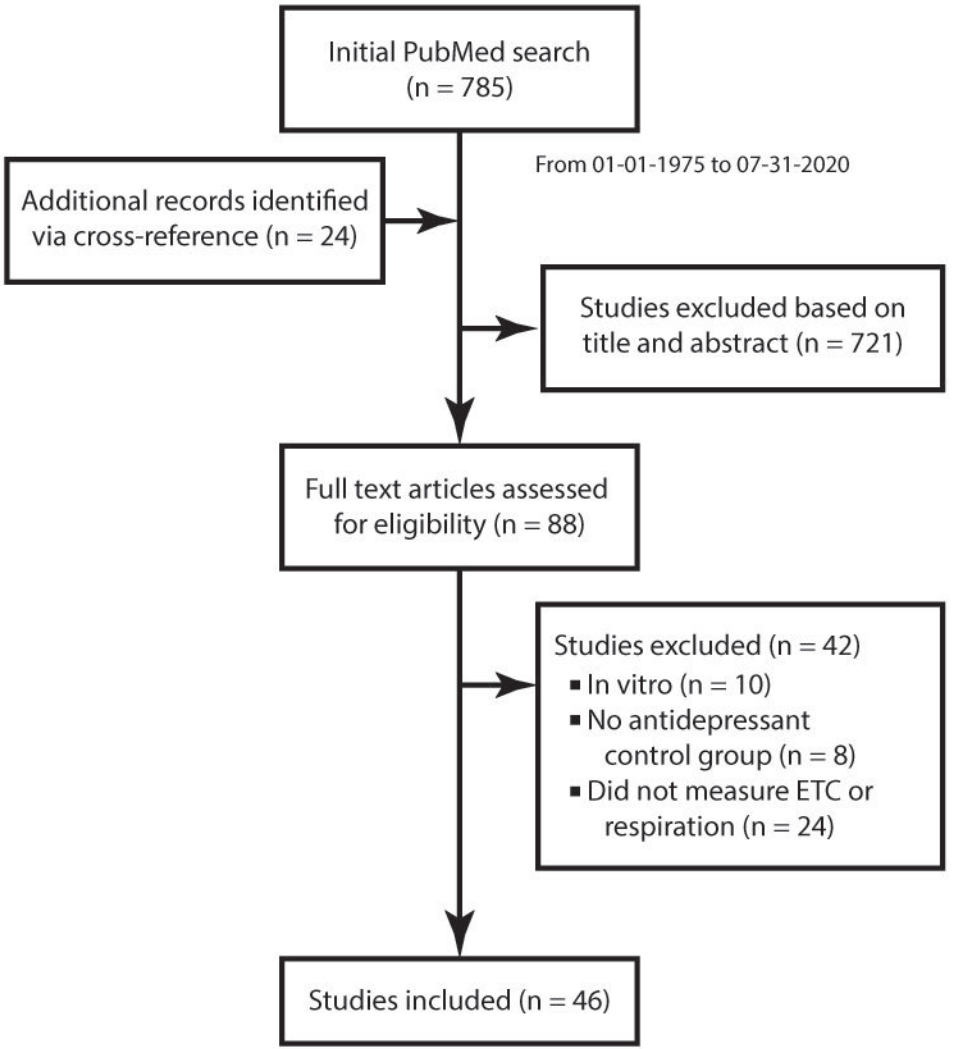
| **Memantine** | | | | | |
| Reus et al. (2012b) | Male Wistar rats<br>60 days old | 5, 10, and 20 mg/kg<br>(ip injection) | Hippocampus<br>Prefrontal cortex<br>Striatum | Acute | CI increased (hippocampus, 5 mg/kg; striatum, 5 mg/kg)<br>CII increased (hippocampus 5 mg/kg)<br>CII-CIII increased (striatum, 5 mg/kg)<br>CIV no effect measured |
| | | | | Chronic (14d) | CI increased (prefrontal cortex, 20 mg/kg),<br>CI decreased (hippocampus, 5, 10, 20 mg/kg; striatum, 10, 20 mg/kg)<br>CII increased (prefrontal cortex, 10 mg/kg; striatum, 10 mg/kg)<br>CII-CIII increased (prefrontal cortex 20 mg/kg; hippocampus, 20 mg/kg; striatum, 10 mg/kg)<br>CIV increased (prefrontal cortex 10 mg/kg; hippocampus, 5 mg/kg; striatum, 5 and 20 mg/kg) |
| **Methylphenidate** | | | | | |
| Fagundes et al. (2007) | Male Wistar rats<br>25 days old | 1, 2, 5, 10, 20 mg/kg<br>(ip injection) | Cerebellum<br>Cortex<br>Hippocampus<br>Prefrontal cortex<br>Striatum | Chronic (28d) | CII increased (cerebellum, all concentrations; prefrontal cortex, 1 and 5 mg/kg)<br>CIV increased (cerebellum, 10 and 20 mg/kg; cortex, 20 mg/kg; hippocampus, 2, 5, 10, and 20 mg/kg; striatum, 5, 10, and 20 mg/kg) |
| Fagundes et al. (2010) | Male Wistar rats<br>25 days old | 1, 2, 10 mg/kg<br>(ip injection) | Cerebellum<br>Cortex<br>Hippocampus<br>Prefrontal cortex<br>Striatum | Acute | CI decreased (cerebellum and prefrontal cortex, all concentrations<br>CII no effect measured<br>CIII no effect measured<br>CIV no effect measured |
| | | | | Chronic (28d) | CI no effect measured<br>CIII no effect measured |

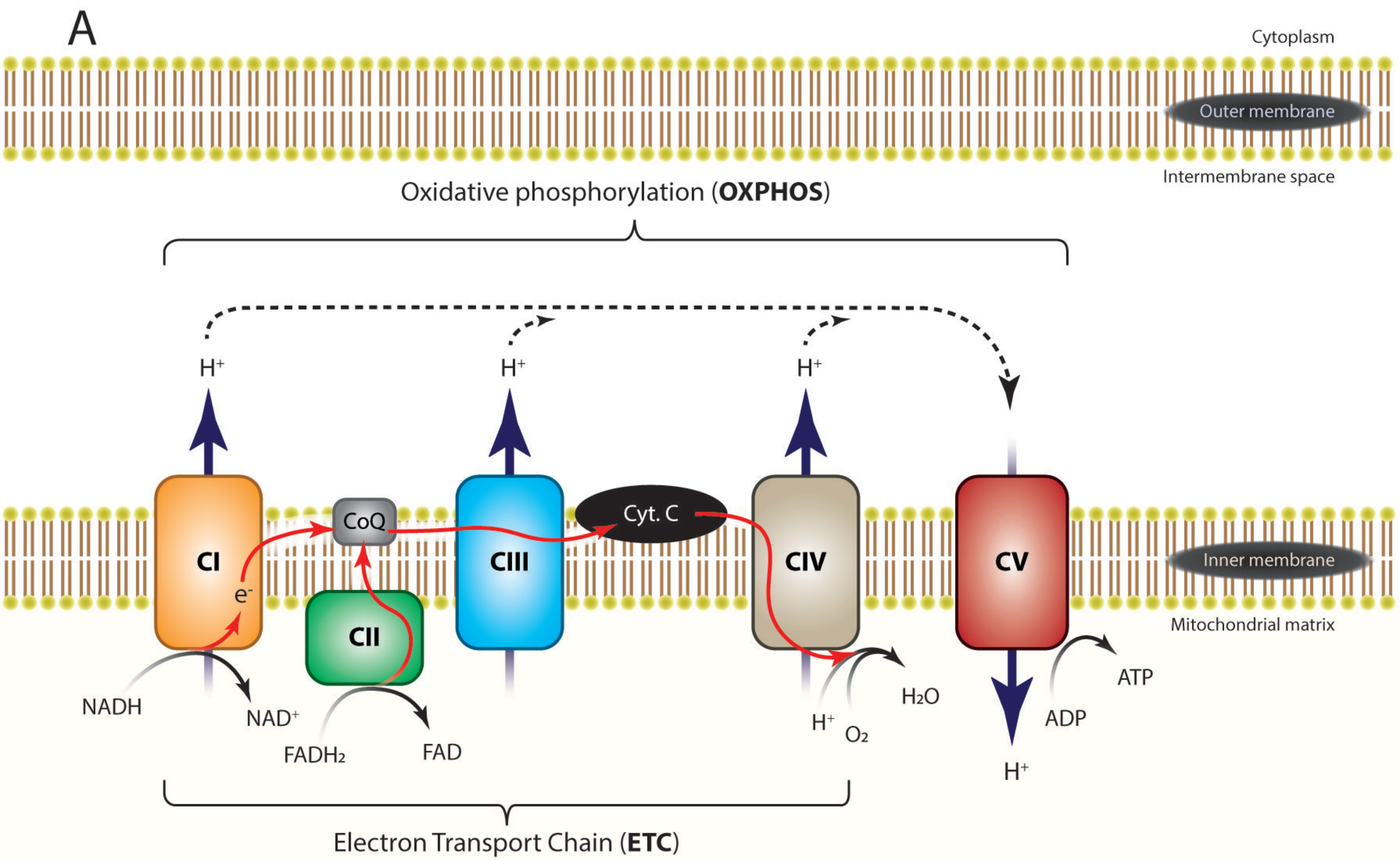
| | | | | | |
|---|---|---|---|---|---|
| **Tianeptine** | | | | | |
| Della et al. (2012) | Male Wistar rats<br>60 days old | 5, 10, and 15 mg/kg<br>(ip injection) | Amygdala<br>Hippocampus<br>Nucleus accumbens<br>Prefrontal cortex | Acute | CS decreased (prefrontal cortex, 10 and 15 mg/kg)<br>CI increased (hippocampus, 5 mg/kg)<br>CII increased (amygdala, 10 and 15 mg/kg; nucleus accumbens, 15 mg/kg)<br>CII-CIII increased (hippocampus, 5 mg/kg)<br>CIV no effect measured<br>MDH no effect measured |
| | | | | Chronic (14d) | CS increased (hippocampus, 5, 10, and 15 mg/kg)<br>CI no effect measured<br>CII increased (hippocampus, 10 and 15 mg/kg)<br>CII-CIII increased (prefrontal cortex all concentrations; hippocampus, all concentrations; amygdala, all concentrations)<br>CIV increased (hippocampus, 10 and 15 mg/kg)<br>MDH increased (amygdala, 10 mg/kg) |
| Della et al. (2013) | Male Wistar rats<br>3 months old | 15 mg/kg<br>(ip injection) | Amygdala<br>Hippocampus<br>Nucleus accumbens<br>Prefrontal cortex | Chronic (14d) | CS increased (hippocampus)<br>CI decreased (prefrontal cortex)<br>CII increased (hippocampus)<br>CII-CIII increased (hippocampus)<br>CIV increased (hippocampus)<br>MDH no effect measured |
| **Valproate** | | | | | |
| Bachmann et al. (2009) | Adult male Wistar Kyoto rats<br>200-250g | Orally, valproate containing food | Brian | Chronic (21d) | CIV no effect measured |
| Valvassori et al. (2010) | Male Wistar rats<br>3-4 months old<br>220-310g | 47.5 mg/kg<br>(ip injection, twice daily) | Hippocampus<br>Prefrontal cortex<br>Striatum | Chronic (7d) | CI no effect measured<br>CII no effect measured<br>CIII no effect measured<br>CIV no effect measured |
| | | | | Chronic 14d | CI no effect measured<br>CII no effect measured<br>CIII no effect measured<br>CIV no effect measured |

| | | | | | |
|---|---|---|---|---|---|
| Feier et al. (2013) | Male Wistar rats 250-300g | 200 mg/kg (ip injection, twice daily) | Amygdala<br>Hippocampus<br>Prefrontal cortex<br>Striatum | Chronic (7d) | CS activity no effect measured<br>CI no effect measured<br>CII no effect measured<br>CII-CIII no effect measured<br>CIV no effect measured<br>MDH no effect measured |
| Streck et al. (2015) | Male C57BL/6 mice 30-35g | 200 mg/kg (ip injection, twice daily) | Cerebellum<br>Cerebral cortex<br>Hippocampus<br>Prefrontal cortex<br>Striatum | Chronic (7d) | CS activity no effect measured<br>CI no effect measured<br>CII increased (cerebral cortex)<br>CII-CIII no effect measured<br>CIV no effect measured<br>MDH no effect measured |

CI = mitochondrial complex I; CII = mitochondrial complex II; CIII = mitochondrial complex III; CIV = mitochondrial complex IV; CS = citrate synthase; ip = intraperitoneal; MDH = malate dehydrogenase.


Initial PubMed search
(n = 785)
From 01-01-1975 to 07-31-2020
Additional records identified via cross-reference (n = 24)
Studies excluded based on title and abstract (n = 721)
Full text articles assessed for eligibility (n = 88)
Studies excluded (n = 42)
In vitro (n = 10)
No antidepressant control group (n = 8)
Did not measure ETC or respiration (n = 24)
Studies included (n = 46)

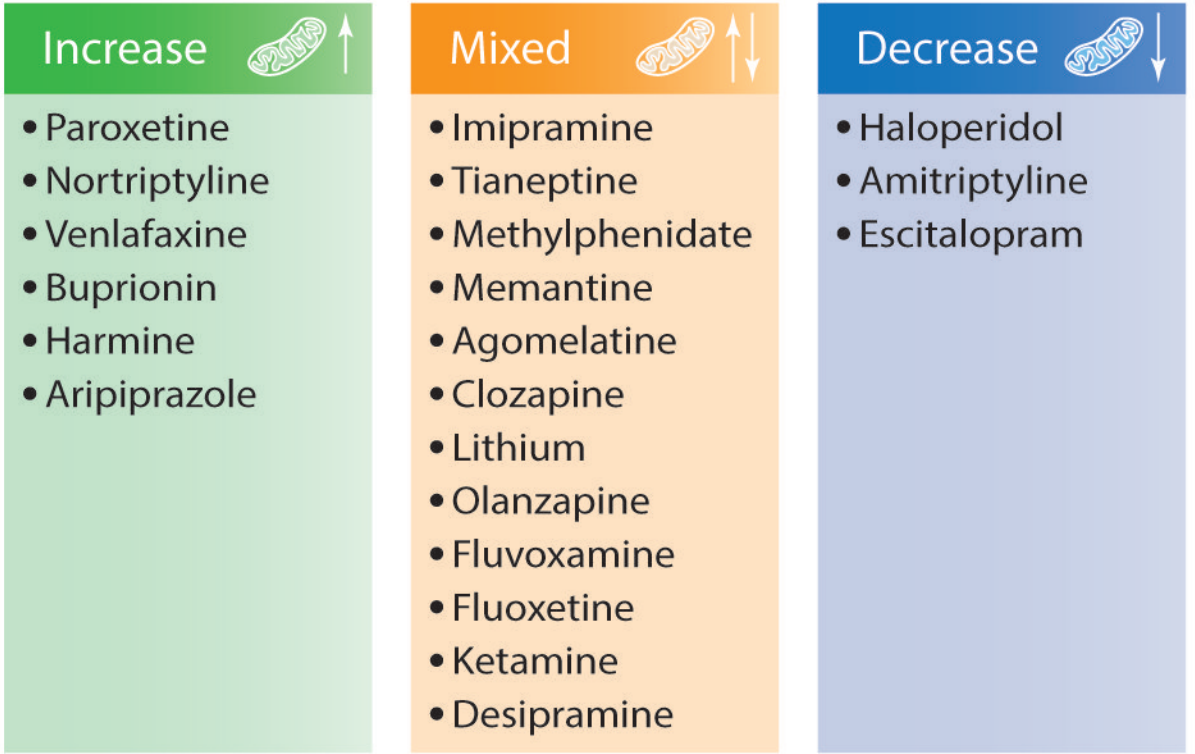
A




B

| Antidepressant | CS | CI | CII | CII-CIII | CIII | COX | State 3 | State 4 | MDH | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Paroxetine | + | + | + | ~ | o | + | o | o | o | 1, 2 |
| Nortriptyline | ~ | + | + | ~ | o | + | o | o | o | 1, 2 |
| Venlafaxine | ~ | ~ | + | ~ | o | + | o | o | o | 1, 2 |
| Bupropion | ~ | ~ | + | ~ | o | ~ | o | o | ~ | 3 |
| Harmine | o | + | ~ | ~ | o | + | o | o | o | 4 |
| Aripiprazole | o | o | o | o | o | ~ | o | o | o | 5 |
| Valproate* | ~ | ~ | ~ | ~ | ~ | ~ | o | o | ~ | 6-9 |
| Imipramine | + | / | + | + | o | + | + | + | o | 4, 10-14 |
| Tianeptine | + | / | + | + | o | + | o | o | + | 13, 15 |
| Methylphenidate | o | / | + | o | ~ | + | o | o | o | 16, 17 |
| Memantine | o | / | + | + | o | + | o | o | o | 12 |
| Agomelatine | o | / | + | o | o | / | o | o | o | 18, 19 |
| Olanzapine | + | + | + | + | o | - | o | o | o | 5, 20, 21 |
| Clozapine | o | ~ | - | o | o | + | o | o | o | 5, 22, 23 |
| Lithium | ~ | ~ | ~ | ~ | ~ | / | o | o | ~ | 6-9, 24-26 |
| Fluvoxamine | / | / | + | - | o | - | o | o | - | 27 |
| Ketamine | o | / | + | / | ~ | ~ | - | / | ~ | 28-32 |
| Fluoxetine | + | / | - | - | o | / | + | + | / | 20, 21, 33-43 |
| Desipramine | + | o | - | o | o | / | o | o | - | 34, 36 |
| Haloperidol | o | - | o | o | o | / | o | o | o | 5, 22, 23 |
| Amitriptyline | o | o | o | o | o | - | o | o | o | 44 |
| Escitalopram | ~ | - | - | - | o | ~ | o | o | ~ | 45, 46 |

+ Increased activity
- Decreased activity
/ Mixed results
~ No effect observed
o Specific complex not measured


Increase
• Paroxetine
• Nortriptyline
• Venlafaxine
• Buprionin
• Harmine
• Aripiprazole
Mixed
• Imipramine
• Tianeptine
• Methylphenidate
• Memantine
• Agomelatine
• Clozapine
• Lithium
• Olanzapine
• Fluvoxamine
• Fluoxetine
• Ketamine
• Desipramine
Decrease
• Haloperidol
• Amitriptyline
• Escitalopram