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Psychotropic medication effects on cortisol: Implications for research and mechanisms of drug action

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ABSTRACT

Stress and the hypothalamic-pituitary-adrenal (HPA) axis have been implicated in the etiology of a range psychiatric disorders; abnormalities in cortisol secretion are well documented in mood, anxiety, and psychotic disorders. There is, however, evidence that psychotropic medications affect HPA function, and are often a confound in research on the relation of cortisol secretion with psychiatric symptoms and syndromes. Psychotropic effects are particularly problematic in longitudinal research on individuals at clinical high risk (CHR) for serious mental illness, because they have the potential to obscure neurobiological mechanisms involved in crossing the threshold from CHR states to clinical disorders. This paper reviews the research literature on the relation of cortisol secretion with the three major classes of psychotropic medication that are most often prescribed; antipsychotics, antidepressants, and stimulants. The studies included in this review are those that measured both baseline and post-treatment cortisol. Taken together, most studies of antidepressants find that they are associated with a reduction in both basal and post-dexamethasone-CRH (DEX/CRH) cortisol, although some report no change. Similarly, antipsychotics, both typical and atypical, are found to reduce basal and DEX/CRH cortisol levels in most studies. Psychostimulant medications, in contrast, are associated with an increase in basal cortisol levels or no change. Effects of psychotropics on the cortisol awakening response (CAR) are less consistent. Implications of these effects for clinical research, especially studies of CHR populations, are discussed. Limitations of the research, due to variations in sample demographic and methodologic factors, are noted, and directions for future research are proposed.

1. Introduction

Stress exposure has been implicated in the etiology of numerous psychiatric disorders, including psychoses (Jones and Fernyhough, 2007; Pruessner et al., 2017), mood disorders, and anxiety disorders (Vreeburg et al., 2010). It is generally assumed that preexisting vulnerabilities can confer sensitivity to the adverse effects of stress, and that the hypothalamic-pituitary-adrenal (HPA) axis plays a role in mediating the relation of stress with psychiatric symptoms. In primates, the HPA axis governs the release of the glucocorticoid, cortisol, for which there are receptors throughout the brain which play an important role in the feedback mechanisms regulating activity of the HPA axis (McEwen et al., 2016; Sapolsky et al., 1990). Persistently elevated glucocorticoids can have adverse effects on brain structure and these findings have fueled interest in HPA function in serious mental illness (McEwen et al., 2016). These organizational effects are mediated by multiple processes, including epigenetic modulation of brain circuitry. Thus the potentially pervasive and sustained effects of cortisol release are assumed to play a role in triggering vulnerabilities to psychiatric disorders (Kalafatakis et al., 2016). It is noteworthy that the brain regions with higher glucocorticoid receptor densities are often functionally and/or structurally abnormal in patients suffering with serious psychiatric disorders, especially psychotic disorders. While most theorizing and empirical research on the etiological role of stress in psychiatric illness has focused on mood and anxiety disorders, there is now a burgeoning scientific literature on stress in psychosis-spectrum disorders. And in recent decades, there is intensified interest in the role of stress and HPA-activity in the prodrome to psychosis. There is now a body of empirical research on HPA function in individuals at clinical high risk (CHR) for psychosis, based on the assumption that dysregulated HPA activity can trigger psychosis (Pruessner et al., 2017). Thus, the neurobiological response to stress is assumed to be one of several neural

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mechanisms in the pathophysiology, acting directly on brain structure/function or indirectly via mechanisms such as neuro-inflammatory pathways. Cortisol is the HPA secretagogue that is the main focus of this research, in part because it is more easily measured in peripheral body fluids than either corticotropin releasing hormone (CRH) or adrenocorticotropic hormone (ACTH).

To date, however, empirical findings from research on cortisol secretion in CHR samples vary, and the research is characterized by diverse samples, methods, and measures (Pruessner et al., 2017). For example, studies of CHR samples vary in the source of the specimens for assay (e g., blood, urine and/or saliva), time-of-day of sampling, and the number of samples obtained. Further, there are numerous potential confounds. Among them, psychotropic medication is the most challenging, because in naturalistic studies where medication is not systematically controlled, it is likely to covary with the nature and severity of symptoms. At enrollment in research protocols, many who meet CHR criteria have a history of mood and attention deficit disorder diagnoses (Kline et al., 2018), and many are on one or more psychotropic medication at baseline and/or previously (Woods et al., 2013). To the extent that HPA activity is causally related with symptom/syndrome severity, and that both are modulated by psychotropic medication, this poses significant problems for reliably measuring HPA secretagogues and their relation with symptoms.

A better understanding of the effects of psychotropic medication on HPA function is critical to both our analytic approaches and etiologic models. If psychotropics have a modulating effect, they must be accounted for in research on the associations between HPA function and psychiatric risk. Further, given the rise in psychotropic medication prescriptions over the past decades, these effects will have strong implications for stress research going forward (Steinhausen, 2015). Finally, documented effects of psychotropic medication on HPA function have the potential to highlight mechanisms of action in treatment response that can further inform our models of pathophysiology.

Naturalistic, cross-sectional studies are limited in their ability to detect causal relations between medication and HPA function because medication is not randomly distributed or experimentally controlled. As mentioned, patient symptoms partially determine medication status, and those with more serious symptoms are more likely to be on multiple classes of psychotropics (antidepressants, antipsychotics) either simultaneously or in succession. Further, if cortisol elevations are partially contributing to symptom severity, then the likelihood of psychotropic prescriptions or dosage changes will be greater for those with higher pre-treatment cortisol levels (Drozdowicz and Bostwick, 2014; West and Kenedi, 2014). Thus medication may potentially confound relations of cortisol with symptom severity and progression. Given the limitations of cross-sectional designs, the focus of the current review is on the relationship between psychotropic medication and HPA-function in studies that measure pre-post-medication levels of HPA secretagogues or studies that experimentally-manipulated medication. Further, we focus on the three main classes of psychotropics that are most commonly prescribed to CHR individuals; antipsychotics, antidepressants, and stimulants (Woods et al., 2013).

The studies for this review were obtained by multiple searches on PubMed using all possible combinations of two categories of keywords; 1) HPA secretagogues (i.e., cortisol, ACTH, CHR or glucocorticoid) and 2) medication terms (i e., antidepressant, antipsychotic, and simulant, and the specific names of drugs in these classes). Inclusion criteria were the use of human subjects, and information on sample size, demographics (age and sex), diagnoses, medication type, and cortisol measurement and assay procedures. Not all reported medication dosage. The findings reviewed below are organized by medication type and study design (longitudinal non-experimental versus longitudinal experimental studies). The study characteristics and key findings from the 30 studies meeting criteria are summarized in Table 1.

Meta-analysis was not conducted given the significant variation in the study measures and methodologies. Studies vary in specimen sampling (i e., blood, saliva, urine), and there is some evidence that blood sampling yields less reliable cortisol estimates than saliva and urine (Fischer et al., 2017). They also differ with respect to the time of day and frequency of sampling and measure of HPA-function. While most measure basal and/or diurnal cortisol, using radioimmunoassay or ELISA (enzyme-linked immunosorbent assay), some measure the cortisol awakening response (CAR) or use a pharmacological challenge such as the Dexamethasone Suppression Test. The CAR is a period of increased cortisol secretion starting soon after morning awakening and peaking 30–45 min post awakening (Stalder et al., 2016). It is typically assessed by obtaining saliva samples immediately after waking, and then at intervals over the next hour. CAR has been viewed as an important aspect of HPA-axis function because it is presumed to be regulated differently from cortisol output the rest of the day, but reliable measurement of CAR is affected by numerous methodological factors (Steptoe and Serwinski, 2016).

Finally, some studies have used a pharmacologic challenge, the Dexamethasone Suppression test (DST) or the Dexamethasone/CRH (DEX/CRH) test to measure HPA activity. Dexamethasone is a steroid that acts through negative feedback to the pituitary gland to suppress the secretion of ACTH, thus typically decreasing cortisol. It is often used in diagnostic protocols (e g., for Cushing's), but also for research on HPA function in other patient populations. Subsequently, the combined dexamethasone suppression/CRH-challenge test was developed. It combines the DST with corticotropin-releasing hormone (CRH) administration (the DEX/CRH test), and shows more reliable test results than DST alone (Deuschle et al., 1998). The DEX/CRH test typically involves the administration of 1.5 mg of DEX at night, then the administration of CRH and repeated measurement of ACTH and/or cortisol. In healthy subjects, DEX administration suppresses the pituitary–adrenal response to CRH, thus lowering both ACTH and cortisol, but post-DEX/CRH hormones are often higher in psychiatric patients than healthy controls.

2. Review of the findings by drug class

2.1. Antidepressants

All four of the major classes of antidepressants have been examined for their effects on HPA function: 1) selective serotonin reuptake inhibitors (SSRIs) which primarily increase extracellular serotonin levels by limiting reuptake, 2) the serotonin and norepinephrine reuptake inhibitors (SNRIs) that reduce the reuptake of serotonin and norepinephrine, 3) tricyclic antidepressants (TCAs) that block the serotonin and norepinephrine transporter, resulting in increased levels of these neurotransmitters, and 4) the tetracyclics (TECAs) which primarily block the serotonin 5-HT2 receptors similar to TCAs.

Compared to other psychotropics, there is a much larger body of research on antidepressants and HPA function, largely because HPA dysregulation has played such a prominent role in theorizing about the etiology of depression. A 2010 meta-analyses (n = 34) evaluated antidepressant effects on cortisol in patients with unipolar depression, focusing on studies that measured pre and post-treatment basal and/or post-DST cortisol (McKay and Zakzanis, 2010). The results showed that all of the antidepressant classes examined (SSRIs, SNRIs, TCAs, and TECAs) significantly reduced basal cortisol and/or the DST cortisol, with a mean effect size of 0.73. Smaller effect sizes for decreases in pre–post ACTH were observed (mean effect size = 55). There were no significant differences among the antidepressant subtypes in the magnitude of the

cortisol or ACTH reductions. The effect sizes for pre/post Hamilton Depression scale (HAM-D) reductions were significantly positively correlated with cortisol effect sizes, but not ACTH. Reports published after this meta-analysis are reviewed below.

2.2. Nonexperimental studies

Several subsequent studies have examined the effect of antidepressant treatment on basal levels of cortisol. Hinkelmann et al. (2012) examined the relationships between salivary cortisol secretion, symptom change, and cognition in depressed patients (n = 52) during 3 weeks of SSRI treatment (escitalopram). Salivary cortisol levels (sampled 4 times per day) and cognitive function were measured pre-and post-treatment in patients, as well as healthy controls (N = 50) matched on demographic characteristics. SSRI treatment was associated with reduced cortisol secretion in patients and post-treatment basal levels were comparable to that of the healthy controls. Notably, the magnitude of the reduction in HAM-D symptom scores was correlated with decreases in cortisol ($r = 0.52$, $p < 01$). Cortisol reduction was also correlated with improvements in some (i e., Auditory Verbal Learning Test and Trail Making Task A and B), but not all, cognitive measures. In contrast, Piwowarska et al. (2012) found no main effect of SSRI treatment (fluoxetine) on blood plasma cortisol levels over 8 weeks of treatment in patients with major depression (n = 21). However, in patients who showed a 50% reduction in symptoms (measured by HAM-D), there was a significant reduction in cortisol secretion over time.

Kopczak et al. (2015) examined the effects of multiple classes of antidepressants (SSRI, SNRI, TCA, and mirtazapine, a TeCA) on basal plasma cortisol in depressed patients at admission and after 6 weeks of treatment. As measured by the HAM-D, there were no significant differences between remitters (n = 39) and non-remitters (n = 39) in antidepressant type or basal cortisol levels at admission. There were also no significant differences in medication changes during the 6-week treatment period. Over the course of treatment both groups showed a significant decline in cortisol, with no difference between remitters and non-remitters in the magnitude of the decline. Differences among antidepressant subtypes were not tested.

Several studies examining the effects of antidepressants on CAR have also found evidence of changes, although the approaches to measuring CAR vary. Beck et al. (2015) examined salivary CAR change over the course of 10 days of SNRI treatment (duloxetine; 90 mg/day) in patients with major depression (n = 12). There was no significant reduction in the CAR area under the curve (AUC) in the total patient sample over the 10 day period. However, there was a significant decrease in CAR AUC among patients who went on to meet remission criteria after 6 weeks of treatment. In regression analysis, patients with a greater *decrease* in CAR showed a greater decrease in HAM-D scores.

Ruhé et al. (2015) measured multiple indices of salivary cortisol response to 12 weeks of SSRI treatment (paroxetine) in depressed patients (n = 70). Cortisol measurements included baseline cortisol levels (BCLs) at awakening, CAR (saliva cortisol level measured at 30 ± 10 min after awakening minus the BCL) and the AUC (BCL + 1/2*CAR). There were no differences between healthy subjects and depressed patients in cortisol measures at baseline. After 12 weeks, patients showed significant decreases in BCL and AUC, although these changes did not vary by remission status. In contrast with Beck et al. (2015), there was an increase in CAR *among* remitters, but no change in non-remitters.

As described above, another common approach in to examining the effects of medication on HPA function has been the use of the DEX/CRH test. Bschor et al. (2012) examined the effects of SSRI treatment (citalopram) on DEX/CRH responsivity and baseline plasma cortisol levels in patients with depression (n = 30). The DEX/CRH test was administered at baseline and after 28 days of treatment. Most patients showed symptoms improvement and/or achieved remission. ACTH levels decreased over the course of treatment. While CRH-stimulated cortisol concentrations declined, they did not show a significant reduction. Interestingly, baseline cortisol increased over the course of treatment. The trend in the DEX/CRH results with citalopram are generally consistent with other studies (McKay and Zakzanis, 2010), although the increased basal cortisol is not.

2.3. Experimental studies

We turn now to experimental designs that have either compared the effects of antidepressants to other drugs or to placebo. Ninan et al. (2014) examined the effects of desvenlafaxine (50 mg/day; SNRI) and a placebo on salivary cortisol in a large double-blind controlled trial of patients with major depression (n = 427). Salivary cortisol was measured at baseline and after 12 weeks of treatment. No significant treatment effects on cortisol were found in comparison with placebo across both responders and nonresponders. However, desvenlafaxine treatment was associated with a significant reduction in HAM-D scores compared to placebo.

Scharnholz et al. (2010) conducted a randomized open-trial comparing a SNRI, venlafaxine, with a TECA, mirtazapine. Morning and afternoon salivary cortisol were measured in patients with depression (N = 87) at baseline and after a 4-week treatment period. Venlafaxine was not associated with changes in cortisol, however higher baseline cortisol concentrations were associated with a poor response to venlafaxine treatment. In contrast, mirtazapine was associated with reduced cortisol levels, although this effect did not differ for responders and nonresponders.

We found only one controlled study of the effects of antidepressants on cortisol in healthy subjects. Knorr et al. (2012) investigated whether SSRI (esitalopram) treatment reduced salivary cortisol in a randomized, placebo controlled design with healthy first-degree relatives of depressed patients (n = 80). Cortisol measurements included AUC on awakening and multiple daytime salivary cortisol (12:00, 18:00 and 23:00) samples obtained at baseline and four weeks after initiation of treatment with escitalopram or a placebo. Both awakening and daytime AUC were significantly reduced at the end of four weeks on escitalopram, but not placebo. These findings suggest escitalopram has the same effect on cortisol in healthy subjects as that observed in depressed patients (Hinkelmann et al., 2012).

We found only one reported study comparing the effects of an SSRI and an antipsychotic on cortisol. Sarubin et al. (2014) examined the effects of escitalopram (SSRI) and an atypical antipsychotic (quetiapine fumarate extended release –QXR) on HPA axis activity in a randomized clinical trial of patients with major depression (n = 30 in each group). The open-label trial was 5-weeks with either escitalopram (10 mg/day) or QXR (300 mg/day). The DEX/CRH test was administered at baseline, and after 1 and 5 weeks of treatment. Blood cortisol AUC values were measured by sampling at 15:00, 15:30, 15:45, 16:00, and 16:15 h after DEX/CRH administration. Patients with a lower cortisol peak concentration at the week 1 DEX/CRH test, compared to baseline, where designated cortisol "peak improvers". QXR and escitalopram resulted in similar reductions in HAM-D, but differed in their effect on cortisol. In the QXR group, but not the escitalopram group, a marked decline in cortisol AUC levels was observed after one week of treatment, but showed a partial rise after 5 weeks. Escitalopram transiently stimulated cortisol AUC at week 1, then cortisol AUC levels at week 5 declined so that they were not significantly different from baseline. These effects contrast with two studies above that find a cortisol reduction in response to escitalopram.

Table 1
Study design and results for each medication class.

Study	Drug(s)	Study design	Participants	Cortisol measure	Dependent measure	Results	Other findings
Antidepressants							
Hinkelmann et al., 2012	SSRI (escitalopram)	NL	52 MDD; 50 HC	Salivary	Pre- vs Post-treatment basal cortisol	↓	Reduction in HAM-D symptom scores was correlated with decreases in cortisol ($r = 0.52$, $p < 01$).
Piwowarska et al., 2012	SSRI (fluoxetine)	NL	21 MDD	Plasma	Pre- vs Post-treatment basal cortisol	↓ (remitters only)	
Kopczak et al., 2015	SSRI, SNRI, TCA, TECA	NL	78 MDD; 92 HC	Plasma	Pre- vs Post-treatment basal cortisol	↓	No difference between remitters and non-remitters
Beck et al., 2015	SNRI (duloxetine)	NL	12 MDD	Salivary	Pre- vs Post-treatment CAR	↓ (remitters only)	↓ in CAR correlated with decrease in HAM-D scores.
Ruhé et al. (2015)	SSRI (paroxetine)	NL	70 MDD; 51 HC	Salivary	Basal cortisol AUC cortisol CAR	↓ Basal and AUC Cortisol ↑ CAR (remitters only)	No difference between HC's and MDD remitters in BL cortisol
Bschor et al., 2012	SSRI (citalopram)	NL	30 MDD	Plasma	DEX/CRH Basal cortisol	↑ Basal cortisol – DEX/CRH	
Ninan et al., 2014	SNRI (desvenlafaxine) vs. placebo	CT	427 MDD	Salivary	Pre vs. Post-treatment basal cortisol	–	
Scharnholz et al., 2010	SNRI (venlafaxine) vs. TECA (mirtazapine)	CT	87 MDD (45 SNRI; 42 TECA)	Salivary	Morning basal cortisol Afternoon basal cortisol	↓ with TECA (afternoon only) – with SNRI	Higher cortisol associated with poorer response to SNRI
Knorr et al., 2012	SSRI (escitalopram) vs. placebo	CT	80 healthy first-degree relatives of MDD patients	Salivary	CAR Daytime AUC cortisol	↓ with SSRI	
Sarubin et al., 2014	SSRI (escitalopram) vs. atypical AP (quetiapine fumarate; QXR)	CT	60 MDD (30 SSRI; 30 AP)	Plasma	AUC cortisol following DEX/CRH test	– with SSRI – with QXR	SSRI transiently increased AUC cortisol at week 1 QXR inhibition of AUC cortisol at week 1; re-increase after week 5
Ventura-Junca et al., 2014	SSRI (fluoxetine) vs. placebo	CT	187 MDD w/ euthyroid	Salivary DST	Pre-vs-post-treatment daytime cortisol	– with SNRI	Both placebo responders and SSRI responders & remitters showed lower cortisol at week 1 than non-responders.
Antipsychotics							
Venkatasubramanian et al., 2010	Atypical AP (risperidone, olanzapine) Typical AP (flupenthixol)	NL	33 AP naïve SZ patients; 33 HC	Serum	Pre-vs-post-treatment basal cortisol	↓ with all APs	SZ patients had higher BL cortisol levels than HC.
Babinkostova et al., 2015	Atypical AP (type not specified) Typical AP (type not specified)	NL	60 SZ; 40 HC	Serum DHEA-S	Pre-vs-post-treatment basal morning cortisol	↓ with all APs	Across all three time points (BL, 3 week post & 6 week post) responders had *higher* serum cortisol and DHEA-S levels than non-responders.
Cai et al., 2018	Atypical AP (type not specified)	NL	147 SZ (FEP & relapsed)	Plasma	Pre-vs-post treatment morning basal cortisol	↓ with APs	SZ patients had higher BL cortisol levels than HC.
Garner et al., 2011	Atypical AP (type not specified)	NL	39 SZ (drug naïve); 25 HC	Plasma, DHEAS Cortisol/DHEAS ratios	Pre-vs-post treatment basal cortisol	–	In first-episode SZ patients, declines in cortisol and the cortisol/DHEAS ratio were associated with reduced symptoms.
Havelka et al. 2016	Atypical AP (risperidone)	NL	23 FEP SZ	Plasma	Pre-vs-post treatment basal afternoon Cortisol DEX Cortisol	↓ in afternoon basal cortisol ↓ DEX cortisol	Decline in cortisol independent of treatment response
Ritsner et al., 2005	One or more antipsychotics within the same medication group	NL	43 SZ	Serum, DHEAS, DHEA, Cortisol/DHEAS ratios	Across treatment (BL, 2 and 4 week basal cortisol)	↑ in cortisol ↑ cortisol/DHEA	Across all three-assessments the responders had a significantly higher cortisol, cortisol/DHEA, and cortisol/DHEAS

(*continued on next page*)

Table 1 (*continued*)

Study	Drug(s)	Study design	Participants	Cortisol measure	Dependent measure	Results	Other findings
						↑ cortisol/DHEAS (responders only)	
Mondelli et al., 2015	Atypical AP (type not specified)	NL	BL and 12-week FU from 24 FEP SZ	Salivary	BL vs post-treatment CAR Basal diurnal cortisol	At first assessment and after 12 weeks, responders had higher CAR when compared with nonresponders	No differences were found in diurnal cortisol levels.
Zhang et al., 2005	Atypical AP (risperidone) Typical AP (haloperidol)	CT	78 SZ; 30 HC	Serum	BL vs post-treatment basal cortisol	↓ with all APs	Risperidone group had lower post-treatment cortisol than haloperidol group. SZ patients had higher cortisol levels than HC at BL and post-treatment. Post treatment cortisol reductions were associated with decreases in symptom severity in SZ patients.
Cohrs et al., 2006	Atypical AP (quetiapine & olanzapine) Typical AP (haloperidol) vs. placebo	CT	11 HC	Plasma	Pre-vs post-treatment AUC cortisol and ACTH	↓ cortisol and ACTH – with Atypical APs – with Typical AP	
Handley et al., 2016	Atypical AP (aripiprazole) typical AP (haloperidol) vs. placebo	CT	17 HC	Salivary	BL vs post-administration cortisol at 1.45 h and 3.10 h	↓ with typical AP (post treatment)	No difference between the placebo and aripiprazole conditions.
Stimulants							
Wang et al., 2014	Methylphenidate (MPH)	NL	40 ADHD children	Salivary, DHEA, DHEA/cortisol	Pre-vs post-treatment (6-month) morning basal cortisol and DHEA	↑ DHEA ↑ DHEA/cortisol – cortisol	
Wang et al., 2017	Methylphenidate (MPH)	NL	50 ADHD; 50 HC	Salivary	BL vs. post-treatment (1, 3 and 6 months) morning basal cortisol	↑ at 1-month in ADHD	Increase in cortisol in ADHD group at 1-month post treatment but decrease to level of HC at 6-month post.
Puig-Antich et al., 1978	Dextroamphetamine vs. phenothiazine	CT	15 ADHD	Plasma	Pre-vs-post treatment (6 months) overnight cortisol	–	
Lee et al., 2008	Methylphenidatevs. Bupropion	CT	22 ADHD	Plasma DHEAS	Pre-vs-post-treatment basal cortisol and DHEAS	– Cortisol ↑ DHEAS	Cortisol did not change in either treatment groups, but DHEAS increased in both.
Dolder et al., 2018	Methylphenidate (MPH), 3,4-Methylenedioxymethamphetamine (MDMA) modafinil	CT	24 HC	Plasma	BL vs. post-administration (1.5 & 2.5 h) basal cortisol	↑ with MDMA – with MPH	
Seibert et al., 2014	MDMA, MPH vs. placebo	CT	16 HC	Plasma	4 separate day cross-over basal cortisol	↑ with MDMA – with MPH	
Oswald et al., 2005	Amphetamine vs. placebo	CT	16 HC	Plasma	Pre-vs post administration (15, 35, and 75 min) basal cortisol	↑ at 15 min ↓ at 75 mins	Plasma cortisol was positively correlated with amphetamine-induced dopamine release in the striatum and putamen.
Hamidovic et al., 2010	Dextroamphetamine vs. placebo	CT	34 HC	Salivary	Pre-vs post administration (30, 60, 90, 120, 180 and 240 min) basal cortisol	↑ with Dextroamphetamine	
Booij et al., 2016	Dextroamphetamine vs. placebo	CT	17 HC	Plasma	Pre-vs-2-weeks post-administration cortisol response to stress	↑ with Dextroamphetamine	Dextroamphetamine treatment also increased stress-induced striatal dopamine release.

AP = antipsychotic; NL = naturalistic longitudinal: CT = clinical trail; MDD = patients with major depressive disorder: HC = healthy controls; SZ = patients schizophrenia; FEP = first-episode psychosis patients; DEX/CHR = post-dexamethasone challenge; BL = baseline; AUC = area under the curve; ↑ = increase in cortisol measure; ↓ decrease in cortisol measure ; – = no change in cortisol measure.

Finally, Ventura-Junca et al. (2014) examined daytime salivary cortisol levels and cortisol suppression by DEX in depressed patients (N = 187) who were treated with placebo for 1 week, followed by treatment with fluoxetine (20 mg) for 2 months. Clinical evaluations were performed before and after placebo treatment, and after 3 and 8 weeks of fluoxetine; cortisol was only measured prior to and following the initiation of fluoxetine treatment. No significant differences were observed between salivary cortisol levels or DST response before and after fluoxetine treatment, independent of treatment outcome. However, both placebo responders and fluoxetine responders and remitters showed lower cortisol at week 1 than non-responders. Thus, consistent with Scharnholz et al. (2010), *higher* cortisol was associated with SSRI nonresponse.

3. Antipsychotics

3.1. Nonexperimental studies

Compared to antidepressants, there have been far fewer studies on antipsychotics and cortisol. Nonetheless, the available findings tend to converge with those on antidepressants in showing a reduction in cortisol.

Venkatasubramanian et al. (2010) examined serum cortisol levels in antipsychotic-naïve schizophrenia patients (n = 33) following three-months of antipsychotic treatment. Patients were treated with either risperidone (n = 17; mean dosage = 4.9 mg/day), olanzapine (n = 14; mean dosage = 10.2), or flupenthixol (n = 2 depot injection of 20 mg every two weeks). Schizophrenia patients had higher cortisol levels than healthy controls (n = 33) at baseline. Following antipsychotic treatment, there was a significant decrease in cortisol levels. There were no reported differences among the antipsychotic subtypes.

Similar findings were observed in a prospective study of schizophrenia patients (n = 60) and healthy controls (n = 40) (Babinkostova et al., 2015). Serum cortisol and dehydroepiadrosterone-sulfate (DHEA-S) levels were measured between 8 and 9 a.m. at baseline and after 3 and 6 weeks of typical or atypical antipsychotic treatment. The schizophrenia patients had significantly higher serum cortisol and DHEA-S levels compared to healthy controls at baseline. Patient cortisol and DHEA-S levels decreased significantly over six weeks of treatment in both responders and nonresponders, as defined by symptom reduction. However, across all three assessments, responders had significantly *higher* serum cortisol and DHEA-S levels compared with non-responders. Interestingly, this pattern is in contrast to the lower levels typically observed in studies of antidepressant responders. The authors report no difference between typical and atypical antipsychotics in their effects, although antipsychotic subtypes were not reported.

In a recent study, Cai et al. (2018) measured the effects of four weeks of atypical antipsychotic treatment on morning plasma cortisol in first-episode and relapsed patients (n = 47) who were medication-free at baseline. Plasma levels of cortisol were significantly higher in patients than controls at baseline, and patient's levels decreased significantly after 4 weeks of treatment. These findings are in contrast with a study which found no baseline differences in cortisol, DHEAS or the cortisol/DHEAS ratio between healthy controls (n = 25) and neuroleptic-naïve or minimally-treated first-episode patients (n = 39) (Garner et al., 2011). After 12 weeks, there were still no group differences in the cortisol measures. However, in first-episode patients, declines in cortisol and the cortisol/DHEAS ratio were associated with reduced positive, negative, and mood symptoms.

A prospective study of the effects of an atypical antipsychotic (risperidone; chlorpromazine equivalent 224.5mg) enrolled 23 consecutive male inpatients with first-episode schizophrenia, and measured afternoon plasma cortisol and post-dexamethasone cortisol prior to and at the end of acute treatment (Havelka et al., 2016). During the period between baseline the end of index hospitalization (mean 43 days, range 10 to 46 days) there were significant declines in basal and post-dexamethasone cortisol levels, as well as positive and negative symptoms. Five patients were classified as cortisol non-suppressors at baseline, but none at the end of treatment. Basal elevated cortisol levels at treatment onset were associated with impaired memory functions.

Although they did not involve pre/post medication measurement, the results of two other longitudinal studies are worth noting with respect to antipsychotic medication. One examined serum cortisol, DHEA(S) and the response to antipsychotic treatment during the exacerbation of psychotic symptoms (Ritsner et al., 2005). Forty three medicated schizophrenia inpatients with acute exacerbation were prescribed stable doses of antipsychotics (one or more typical or atypical antipsychotics within the same class) up to 2 weeks prior to entering the study (baseline), and blood samples were collected again after 2, and 4 weeks. (i e., baseline cortisol and DHEA were not measured pre-medication.) After 4-weeks, patients were classified as responders or non-responders, based on symptom severity. Across all three-assessments (baseline, 2 and 4 weeks) the responders had a significantly higher serum cortisol, cortisol/DHEA, and cortisol/DHEAS ratios, while DHEA(S) concentrations did not differ between the groups. Similarly, a naturalistic longitudinal study by Mondelli and colleagues tested the relation of diurnal salivary cortisol levels and the CAR with treatment response at 12 weeks follow-up in medicated first-episode psychosis patients (Mondelli et al., 2015). Patients were on a variety of antipsychotics. Cortisol was measured in 24 patients at baseline and 12-weeks. At first assessment and after 12 weeks, responders had higher CAR when compared with nonresponders, but there were no differences in diurnal cortisol levels.

3.2. Experimental studies

Zhang et al. (2005) compared the effects of typical and atypical antipsychotics on serum cortisol in schizophrenia patients (n = 78) and healthy controls (n = 30). In this double-blind study patients underwent a 2-week washout, and were then randomly assigned to 12 weeks of treatment with either 6 mg/day of risperidone or 20 mg/day of haloperidol. Patients had significantly higher cortisol levels than healthy controls at both baseline and post-treatment. Patient cortisol levels significantly declined over the course of treatment in both antipsychotic groups, but when the two groups were compared, the risperidone group had a significantly lower post-treatment cortisol compared to the haloperidol group. Cortisol reductions were associated with decreases in symptom severity in both treatment groups.

The suppressing effects of atypical antipsychotics on cortisol have also been observed in healthy subjects. In a double-blind, placebo-controlled, randomized cross-over design of healthy males (n = 11) two atypical antipsychotics - quetiapine (50 mg) and olanzapine (5 mg) - were compared with haloperidol (3 mg) and placebo (Cohrs et al., 2006). Plasma ACTH and cortisol were measured at baseline and over 4 sessions one week apart. When compared to placebo, quetiapine and olanzapine significantly reduced ACTH and cortisol AUC. In contrast, there was no significant effect of haloperidol on cortisol measures.

Finally, it is important to note that there may be differences in the timing of the effects of typical and atypical antipsychotics on cortisol. In a study of the short term effects of antipsychotics on cortisol in healthy subjects (N = 17), Handley et al. (2016) administered haloperidol (3 mg), aripiprazole (10 mg) and placebo, in a randomized order at three study appointments. Salivary cortisol was measured at baseline (10:20 am), and at 1.45 h and 3.10 h post

medication/placebo. There were significantly lower post-treatment cortisol levels in the haloperidol condition than in either the placebo or aripiprazole conditions. There was no difference between the placebo and aripiprazole conditions. These findings suggest that the effects of haloperidol on HPA activity may occur more rapidly. However, the study does not address the potential longer term effects of either antipsychotic on HPA activity.

4. Stimulants

4.1. Nonexperimental studies

In contrast to the effects of antidepressants and antipsychotics, the aggregate findings on stimulant medications suggest an increase or no change in cortisol. Further, as would be expected, the patients in stimulant studies tend to be younger.

A prospective study examined morning salivary levels of cortisol, DHEA, and DHEA/cortisol ratios in children with attention deficit hyperactivity disorder (ADHD; n = 40) while they underwent treatment with methylphenidate (MPH: 5–15 mg/day) (Wang et al., 2014). After six months of treatment with MPH, there were significant increases in salivary DHEA levels and DHEA/cortisol ratios, but no changes in cortisol levels. In a later study by Wang et al. (2017), the effects of MPH on morning salivary cortisol were measured in children with ADHD (n = 50) at baseline and at 1, 3, and 6 months after treatment initiation. In this study, salivary cortisol levels increased significantly after 1 month of MPH, then at 3 months declined from 1-month levels so that they were intermediate between baseline and 3 months, then declined further at 6-months to a level similar to healthy controls.

4.2. Experimental studies

The earliest published experimental study of stimulant effects on cortisol compared dextroamphetamine to phenothiazine (Puig-Antich et al., 1978). Children (ages 6–9 years) who had been under treatment for ADHD were given a 2 week washout period from medication. Intravenous blood samples were obtained overnight every 20 min from 8 pm until 10 am. This procedure was conducted at baseline, and after 1 and 6 months of dextroamphetamine or phenothiazine treatment. Mean plasma cortisol from sleep onset to 10 a.m. showed no significant changes between baseline, 1 month, or 6 months for either medication.

In a similar study, Lee et al. (2008) examined plasma levels of DHEA-S and cortisol in ADHD patients (mean age 12 years) randomly assigned to 12 weeks of either MPH (n = 12) or bupropion (n = 10). Plasma levels of DHEA-S increased significantly over the treatment period, but there was no significant change in cortisol levels.

Dolder et al., 2018 conducted a double-blind, cross-over study of healthy young adults (n = 24) and examined the effects of single doses of MPH (60 mg), 3,4-Methylenedioxymethamphetamine (MDMA) (125 mg), modafinil (600 mg), and placebo on plasma cortisol. Samples were obtained at baseline, 1.5 and 2.5 h after drug administration. Only MDMA was associated with increases in cortisol. This is consistent with a previous study utilizing a cross-over design, in which MDMA (125 mg), but not MPH (60 mg), increased plasma cortisol compared to placebo in a sample of healthy young adults (n = 16) (Seibert et al., 2014).

In contrast to the results of the above investigations, which indicate no stimulant effect on cortisol when measured hours or weeks after administration, there is some evidence that amphetamines acutely increase cortisol and this may occur in conjunction with dopamine augmentation. An experimental study of the effects of amphetamine and placebo on cortisol and dopamine was conducted on a sample of 16 healthy young adults (Oswald et al., 2005). Subjects received intravenous saline or amphetamine (0.3 mg/kg) prior to undergoing two consecutive PET studies to measure dopamine release with high [11C]raclopride. (Dopamine release was indexed as % in raclopride binding between the placebo and amphetamine scans.) Measures of plasma cortisol were obtained prior to and 15, 35, and 75 min post drug. Plasma cortisol was positively correlated with amphetamine-induced dopamine release in the striatum and putamen. Fifteen minutes after amphetamine, there were significant increases in cortisol, and these began to decline at 75 min post-administration.

Similarly, a study of physiological responses (salivary cortisol, heart rate, mean arterial pressure) to dextroamphetamine (20 mg) and placebo administration was conducted on healthy adult volunteers (N = 34) (Hamidovic et al., 2010). Responses were measured at 30, and 60, 90, 120, 180 and 240 min after oral administration. There was no baseline difference between the dextroamphetamine and placebo groups. However, dextroamphetamine significantly increased cortisol levels, as well as heart rate and mean arterial pressure, compared to placebo. The time course of the cortisol increase was not described.

There is also some evidence that stimulant medication increases the cortisol response to stress. In a placebo-controlled study, Booij et al. (2016) examined whether repeated exposure to dextroamphetamine would lead to cross-sensitization, thereby increasing dopaminergic responses to stress. They used PET to measure [11C] raclopride binding responses to a psychosocial stress task in healthy subjects (n = 17) before and two weeks after a regimen of repeated dextroamphetamine or placebo. Prior to the dextroamphetamine regimen, exposure to the stress task was associated with increased behavioral and physiological indices of stress (anxiety, heart rate, and cortisol). Dextroamphetamine exposure was associated with increases in the stress-induced cortisol response.

5. Summary of findings and implications

Understanding the effects of psychotropic medications on the HPA axis is important for research on stress and understanding the neurobiological mechanisms mediating psychiatric illnesses. This is particularly critical for research that aims to identify the mechanisms underlying the progression of subclinical symptoms into serious disorders, such as psychosis. Because CHR youth often experience cognitive mood, and other symptoms, they frequently have a history of psychotropic treatment. Further, due to increases in the prescription of psychotropic medications, especially antidepressants, antipsychotics, and stimulants, the proportion of CHR youth who are prescribed a psychotropic will likely continue to rise (Steinhausen, 2015).

This review focused on studies that examined pre-and-post treatment measures of cortisol. The studies vary in methodology, sample size, and sample characteristics (e.g., clinic status, demographics); all factors that could influence HPA activity. Nonetheless, the results are relatively consistent. Most studies of antipsychotics and antidepressants (with the exception of fluoxetine) tend to yield a reduction in cortisol secretion, whereas investigations of stimulants show either no change or an acute increase. Further, the cortisol declines observed in studies of antidepressants and antipsychotics tend to be associated with decreases in symptoms.

Within drug classes, the empirical data do not provide an adequate basis for drawing inferences about the effects of any particular medication. Among the antidepressants, for example, it appears that SSRIs (e g., escitalopram, paroxetine,), SNRIs (e g., desvenlafaxine, venlafaxine, duloxetine), tricyclics (e.g., amitriptyline, trimipramine), tetracyclics (e.g., mirtazapine) and atypical antidepressants (e.g., tianeptine) can dampen cortisol secretion. Similarly, among the antipsychotics, both typical (haloperidol) and atypical (e g., risperidone, quetiapine, olanzapine) drugs have been

found to reduce HPA activity in one or more studies.

For each class of drugs, there are plausible neural mechanisms that can account for their effects on HPA activity. While it is beyond the scope of this paper to review the evidence supporting various mechanisms, we highlight some dominant assumptions. Stress-induced or genetically-determined hyperactivity of the HPA axis has been hypothesized to trigger or exacerbate clinical symptoms in both depression and psychosis. In depression, this HPA-hyperactivity is thought to result from impaired feedback inhibition by glucocorticoid (GR) and mineralocorticoid (MR) receptors. Antidepressants have been shown to increase GR and MR expression and function thereby enhancing negative feedback of the HPA axis by endogenous glucocorticoids and reduced basal cortisol secretion (Pariante et al., 2004). There are also potential mechanisms involving augmentation of serotonin (Baumeister et al., 2016).

In psychosis, there is evidence of a synergistic relation between dopamine activity and HPA activation, such that there is bidirectional augmentation (Booij et al., 2016; Meltzer et al., 2001; Mizrahi, 2016; Pruessner et al., 2017). Antipsychotics reduce subcortical DA neurotransmission, which likely leads to corresponding reductions in basal and stress-induced cortisol secretion. Stress exposure has also been found to produce changes in dopamine receptors, such that persistent stress may permanently alter the modulation of the HPA axis, which may in turn enhance dopamine release. In the case of stimulants, there is evidence of cross-sensitization effects. That is, exposure to stimulants appears to heighten sensitivity to stress by enhancing dopamine release in striatal areas and producing HPA augmentation (Booij et al., 2016).

Despite the fact that there are plausible mechanisms to account for direct neurobiological effects of psychotropics on HPA activity, it is also important to consider that the effects may be partially mediated by symptom changes. In other words, the reductions in symptom severity that result from treatment with antidepressants and antipsychotics may reduce subjective stress/distress and, in turn, lower cortisol secretion and stress-sensitivity. On the other hand, while it is plausible that longer-term effects of antidepressants and antipsychotics on HPA activity are due to clinical improvement, the rapid reduction in cortisol observed in some studies of these medications suggest that their impact is at least partially a reflection of direct neurobiological modulation of HPA function.

It is also noteworthy that there is evidence that the effects of psychotropics on HPA function differ among patients based on pre-treatment HPA function. For example, several of the studies reviewed above revealed that higher pre-antidepressant cortisol levels were associated with poorer treatment response (e.g., Scharnholz et al., 2010; Ventura-Junca et al., 2014). Consistent with this, a recent meta-analysis from 39 studies of depressed patients that included a pre- and a post-treatment measurement of symptom severity revealed that pre-antidepressant (amitriptyline, citalopram/escitalopram or fluoxetine) urine and salivary cortisol levels were higher in medication nonresponders than responders (Fischer et al., 2017). Cortisol after DEX suppression was also elevated in treatment nonresponders. In contrast to urine and saliva, the meta-analysis showed that blood/plasma levels of cortisol did not discriminate non-responders from responders, suggesting that when cortisol is measured more invasively with blood, group differences can be obscured. Also noteworthy, neither pre-treatment CRH nor ACTH distinguished non-responders from responders. Thus it appears elevated basal cortisol is linked with more treatment-resistant depression.

In contrast, among the studies of antipsychotics reviewed here, the two that reported on pre-treatment cortisol levels and treatment response indicate that elevated cortisol was associated with better response. One study showed that schizophrenia patients had higher cortisol levels in comparison with a control group, and treatment responders had higher baseline cortisol in comparison to non-responders (Babinkostova et al., 2015). The other investigation yielded similar results; antipsychotic treatment responders had elevated initial serum cortisol and cortisol/DHEAS ratios compared with non-responders, and these differences remained significant at the three time-points (Ritsner et al., 2005). Thus, it appears that cortisol elevations in depressed versus psychotic patient samples may differ in their origins, and/or that antidepressants and antipsychotics are affecting HPA activity in different ways. Nonetheless, despite the evidence that pretreatment cortisol levels differentially predict the response to antidepressants and antipsychotics, post-treatment cortisol reductions tend to be positively related with symptom reductions in response to both types of medication.

6. Conclusion and future directions

In summary, the findings reviewed in this paper highlight the importance of psychotropic medication in research on stress and HPA function in clinical populations. Given the reported associations between medication and cortisol, it will be important for future studies to consider these effects in their analytic approaches and interpretation of findings. Though challenging, this can be achieved by including medication status as an independent variable, rather than a covariate, as well as by within-subject studies that involve concurrent longitudinal measurement of changes in medication, HPA function, and clinical symptoms.

The findings also suggest some potentially fruitful avenues for further investigation. Several studies revealed an association between baseline cortisol levels and treatment response to antidepressants and antipsychotics, as well as between the magnitude of symptom reduction and cortisol decline following treatment. This may have important implications for the mechanisms of drug action, as well as predicting the clinical response to treatment. It is clear that the relation of psychotropic treatment with HPA function merits more extensive study. Chief among the questions to be addressed are: 1.) What patient factors (e g., genetic, clinical) determine the HPA response to various classes of psychotropic? and 2.) Do antidepressants and antipsychotics affect the HPA axis via different mechanisms?

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