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Antiglucocorticoid therapy for older adults with anxiety and co-occurring cognitive dysfunction: results from a pilot study with mifepristone

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Abstract

Objectives—In older adults with anxiety disorders, chronically elevated cortisol may contribute to cognitive impairment and elevated anxiety. We conducted a pilot study with mifepristone, a glucocorticoid receptor antagonist, as a potential treatment for late-life anxiety disorders and co-occurring cognitive dysfunction.

Methods—15 individuals aged 60+ with an anxiety disorder plus cognitive dysfunction participated in the 12 week study. In the first week, participants were randomly assigned to mifepristone 300mg daily or placebo. In the subsequent 3 weeks, all participants received mifepristone 300mg. Mifepristone was then discontinued, and the participants were reassessed 8 weeks later. We examined (1) cognitive changes; (2) worry symptom severity; (3) safety and tolerability; and (4) salivary cortisol before, during, and after mifepristone exposure.

Results—Overall safety, tolerability, and high retention supported the feasibility of this research. Participants with higher baseline cortisol levels (peak cortisol >6.0ng/ml, n=5) showed improvements in memory, executive function, and worry severity after 3–4 weeks of mifepristone with persistent memory and worry improvements 8 weeks after mifepristone discontinuation. Individuals with low to normal baseline cortisol (n=8) showed little to no improvement. As expected, cortisol levels rose during mifepristone exposure and returned to pre-treatment levels 8 weeks after mifepristone discontinuation. In the first week of treatment, there were no differences between placebo-treated and mifepristone-treated participants.

Conclusion—The results of this pilot study warrant further testing of antiglucocorticoid agents in late-life anxiety disorders with co-occurring cognitive dysfunction. Mifepristone is hypothesized to have benefits in patients with evidence of glucocorticoid excess. Directions for further study are discussed.

Keywords

anxiety; elderly; glucocorticoid; mifepristone; stress; memory

Introduction

Anxiety disorders may cause cognitive dysfunction in older adults (Beaudreau and O'Hara, 2008). In older adults with psychiatric illness such as anxiety disorders and depression, cognitive dysfunction is associated with increased disability (Butters et al., In Press, Alexopoulos et al., 2002, Middleton and Yaffe, 2009, Gallo et al., 2003, Butters et al., 2011) increased health care utilization (Mackin et al., 2011) and diminished treatment response (Butters et al., In Press, Caudle et al., 2007, Alexopoulos et al., 2005, Sneed et al., 2010, Potter et al., 2004, Story et al., 2008). The common pharmacotherapies for anxiety in late-life – benzodiazepines and antidepressants – have limited benefit and may worsen cognitive function (Butters et al., In Press, Pomara et al., 1989, Pomara et al., 1998, Foy et al., 1995, Hanlon et al., 1998, Paterniti et al., 2002). Additionally, while Cognitive Behavioral Therapy is effective for late-life anxiety disorders (Wetherell et al., 2013, Stanley et al., 2009), it is less effective in the context of cognitive impairment (Caudle et al., 2007). Safe, rationally-selected, novel pharmacologic treatments are needed that target anxiety-related cognitive impairment (Wilkins et al., 2010).

A hypothesis relevant to geriatric anxiety concerns the role of excess glucocorticoid exposure in aging (Sapolsky et al., 1986, McEwen and Sapolsky, 1995, Lupien et al., 2007). According to this model, prolonged excessive stress (such as chronic excessive anxiety) combined with age-related loss of inhibitory inputs produces excessive activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, elevating cortisol levels. Increased cortisol levels may compromise vulnerable neurons in brain regions including the hippocampus and dorsolateral prefrontal cortex (dlPFC) (Green et al., 2006, Rothman and Mattson, 2010, Rissman et al., 2007, Li et al., 2010, Joshi et al., 2012, Sotiropoulos et al., 2011, Yao et al., 2011, Zhang et al., 2011) which have a high density of glucocorticoid receptors (Sarrieu et al., 1986). These changes lead to synaptic loss, neuronal dysfunction, and potential atrophy of the hippocampus and dlPFC, with associated dysfunction of related brain networks and of memory and executive functioning (Ferrari and Magri, 2008). Supporting these experimental preclinical studies are observational studies linking HPA axis hyperactivity to cognitive impairment and decline in older adults (Beluche et al., 2010, Comijs et al., 2010, Csernansky et al., 2006, Fiocco et al., 2006, Gerritsen et al., 2009, Karlamangla et al., 2005, Lee et al., 2007, Li et al., 2006, Lind et al., 2007, Lupien et al., 1994, Lupien et al., 1998, Lupien et al., 1999, O'Brien et al., 2004, Yehuda et al., 2007).

Additionally, HPA axis dysfunction may be associated with persistent anxiety, possibly because impairment in these cognitive domains contributes to treatment-resistance in anxiety disorders (Caudle et al., 2007) or because HPA dysfunction directly interferes with the effects of antidepressants (Young et al., 2004b, Juruena et al., 2009, Ising et al., 2007). HPA axis hyperactivity is seen in late-life anxiety disorders such as GAD (Chaudieu et al., 2008, Lenze et al., 2010, Mantella et al., 2008). We previously showed that elevated cortisol

in late-life GAD is lowered with successful SSRI pharmacotherapy (Lenze et al., 2010), with associated improvements in immediate and delayed recall (Lenze et al., 2011). These findings suggest that reducing HPA axis hyperactivity could improve cognitive functioning in late-life anxiety disorders. Since HPA hyperactivity appears to attenuate the effects of SSRIs on serotonergic transmission (Gartside et al., 2003), it may be ideal to directly block the effects of excess cortisol.

Mifepristone, a GC receptor blocker, reverses the toxic effects of GC excess at CNS structures and their cognitive consequences (Joels, 2011, Matrisciano et al., 2011, Hu et al., 2012). Mifepristone is FDA-approved for the treatment of Cushing's syndrome (a condition of supraphysiologic cortisol typically due to pituitary tumor) and improves cognitive impairment in that syndrome (Fleseriu et al., 2012). Mifepristone has also been examined in other psychiatric conditions with putative HPA dysfunction such as psychotic depression, bipolar disorder, schizophrenia, and PTSD (Blasey et al., 2011, Gallagher et al., 2008, Gallagher et al., 2005, Golier et al., 2012, Watson et al., 2012, Young et al., 2004a). We therefore carried out a pilot study of mifepristone in late-life anxiety disorders. We hypothesized that mifepristone would be safe and well-tolerated during 3–4 weeks of treatment and would improve memory, executive functioning, and worry symptoms, specifically among patients with high baseline cortisol levels.

Methods

Participants aged 60 and older, with a current anxiety disorder (generalized anxiety disorder, panic disorder, or anxiety disorder not otherwise specified) as diagnosed by the Structured Clinical Interview for Axis I disorders (First et al., 1997), were recruited from a pool of well-characterized patients who had participated in previous clinical trials or were under psychiatric care. All participants also had subjective reports of cognitive impairment as captured by the PROMIS-cognitive concerns short form scale (www.nihpromis.org). Exclusion criteria were: known diagnosis of dementia, lifetime psychotic or bipolar disorder, active substance abuse (within past 6 months), unstable medical condition, current or recent corticosteroid use, or any condition or medication that was a contraindication to mifepristone use (such as simvastatin). Comorbid major depressive disorder was allowed (as long as the anxiety disorder was principal or co-principal diagnosis). The local institutional review board approved the project, and all participants provided informed consent prior to any research participation.

The study was 12 weeks long. In the first week of the study, participants were randomly assigned (1:1) to either mifepristone 300mg orally daily or matching placebo; this was done to test the feasibility of using a placebo-controlled design, in preparation for future studies. After this first week, all participants received mifepristone 300mg daily for three weeks; this time frame was chosen based on achieving steady-state concentration of mifepristone. Thus, by week 4, all participants had received mifepristone for 3 weeks (if initially randomized to placebo) or 4 weeks (if initially randomized to mifepristone). The 300mg dose is lower than in other studies in psychiatry (most studies used 600–1200mg), based on the older age of the participants and the longer duration of treatment. At week 4, mifepristone was stopped and participants were re-assessed eight weeks later.

Thus, there were four assessment points: week 0 (pre-treatment), week 1 (end of placebo-controlled phase), week 4 (end of open-label mifepristone phase), and week 12 (off-treatment). The primary endpoint was the week 4 assessment of cognition and anxiety symptoms.

At each assessment point participants were assessed for memory and executive function. The two memory measures were a 16-word list recall similar to the Rey auditory verbal learning test, which has been used by the Washington University Alzheimer's Disease Research Center; and two paragraphs from a set of paragraph recall tests validated as sensitive to effects of stress-level glucocorticoids (Newcomer et al., 1994). In these memory measures, the key outcomes are immediate and 20-minute delayed recall. For each memory variable, a z score was computed for each participant, where $z \text{ score} = (\text{participant score} - \text{mean}) / \text{standard deviation}$. Then a single composite memory variable was created by summing up these z scores. The two executive function tests were the color-word interference test, in which the key variable was number of errors made in condition 4 (inhibition/switching task; the Delis-Kaplan Executive Function Scale (Delis et al., 2001)) and the Letter Number Sequencing task, for which total correct trials was the key variable. For each of these two variables, a z score was computed for each participant, and the z scores for the two variables were then summed for each participant. To measure anxiety changes, participants provided self-report assessments of worry at each key assessment point with the Penn State Worry Questionnaire-Abbreviated (Hopko et al., 2003), an 8-item measure (range 8–40) that has been used to measure symptomatic change in late-life anxiety treatment studies. We assessed safety and tolerability at all time points by systematically enquiring about symptoms of adrenal insufficiency and any side effects, as well as week 0 and week 4 measures of electrolytes, thyroid stimulating hormone, and complete blood count.

We measured cortisol in saliva, which participants collected at home three times daily – immediately upon awakening, 30 minutes after waking, and at bedtime – for three consecutive days at baseline and at weeks 4 and 12. This method has been shown to provide a reliable marker of adrenocortical activity in humans (Pruessner et al., 1997), and saliva level correlates highly (0.91) with serum cortisol (www.salimetrics.com). Collection was done by participants at their home, not directly supervised by researchers; detailed methods to maximize adherence and accuracy of collection, including self-report diaries and reminder calls, and of assay information, are published elsewhere (Mantella et al., 2008). We examined cortisol levels for three reasons: first, to demonstrate central “target engagement” with this dose of mifepristone, which would be reflected with a significant increase in peripheral cortisol from baseline to week 4 (reflecting reduced feedback inhibition from mifepristone's blockade of CNS GC receptors); second, to determine whether these increased cortisol levels normalized by week 12; and third, to explore if baseline cortisol levels predicted improvement with the cognitive or anxiety measures. Specifically, we hypothesized that mifepristone-induced improvements in cognitive function and anxiety would be isolated to only those with baseline evidence of glucocorticoid excess. We chose a cutoff of peak cortisol of 6.0 ng/ml, or >2 standard deviations above a sample of healthy, nonanxious comparisons (Mantella et al., 2008). Because of the small sample size, no inferential statistics were carried out on outcome measures.

Results

Between September-December 2012, 15 participants participated in the study. All 15 completed the week 1 assessment; 2 dropped out prior to completing the week 4 assessment, and one more dropped out prior to completing the week 12 assessment. Demographic and baseline clinical data of the sample are as follows: age, mean 73.1 (SD 9.1); 73% female; 87% white, 13% African-American; 14 had current Generalized Anxiety Disorder and 1 had current Panic Disorder; 4 also had a diagnosis of current Major Depressive Disorder (two each in the high and low cortisol groups). Participants' cognitive test scores were (mean $\pm$ SD, range shown): immediate list learn (sum of four trials of 16-word list), 26.2 (8.9, 13–42); delayed list recall (after 20 minute delay), 5.4 (4.0, 1–14); immediate paragraph recall (out of 88 points total both paragraphs combined): 33.7 (16.1, 8–59); delayed paragraph recall (after 30 minute delay): 29.6 (17.4; 0–56.5); letter-number sequence (how many correct trials, maximum 21): 9.0 (3.0; 4.0–14.0); Color-Word interference test errors: 7.6 (8.0; 0–28); these results show that the sample had a wide range of cognitive function. Baseline Cumulative Illness Rating Scale (Miller et al., 1992) score was 9.9 (SD 3.6), indicating moderate medical comorbidity. All participants were euthyroid at baseline. Baseline Penn State Worry Questionnaire-Abbreviated score was 28.6 (SD 6.6); for reference, the threshold for older adults with GAD is 22 (Stanley et al., 2003) while the mean score in healthy older adults is 15 (Crittendon and Hopko, 2006). Coprescribed antidepressant medications are listed in supplementary table 1; two participants were taking benzodiazepines at baseline (alprazolam at stable dose throughout study): 0.25mg daily for one, 0.25mg four times daily for the other; both were in the high baseline cortisol group.

Tolerability and safety outcomes

(a) Dose-limiting side effects were minimal: dizziness (n=1) which improved with reduction to 150mg. (b) Other side effects were transient and mild (dizziness most common [n=5], followed by fatigue [n=3] and nausea [n=2]). None developed overt signs of adrenal insufficiency (i.e., severe fatigue, muscle weakness, loss of appetite, hyperpigmentation). (c) Safety testing included metabolic and hematological variables and showed no serious or unanticipated adverse events; one participant developed a drop in neutrophil count (from 3 to 1.8K) with no clinical sequelae; two developed very mild hypokalemia (K=3.4 for both); one had a small drop in thyroid T4 level (0.89 to 0.75); and one had worsening of pre-existing orthostatic hypotension. None developed an infection, anemia, eosinophilia, or hypoglycemia, which are potential side effects of glucocorticoid receptor antagonism.

Results from placebo-controlled phase

There were no observed effects suggesting improvement in cognitive function or anxiety with mifepristone relative to placebo, and sample sizes were too low (n= 2 and 3 in mifepristone and placebo groups, respectively) to examine group differences in improvements in only those with high baseline cortisol.

Outcomes at week 4 and 12

Figure 1 shows changes in memory scores, executive function scores, and PSWQ-A scores, with the sample dichotomized by baseline cortisol level based on the previously-mentioned baseline cortisol cutoff of 6.0 ng/ml to define high vs. low-to-normal peak cortisol.

At week 4 (end of mifepristone open-label treatment), the participants with baseline peak cortisol >6.0ng/ml (n=5) showed improvements in all of these domains, while the participants without high baseline cortisol (n=8) showed less or no improvement. Figure 1 shows the changes in scores. Effect sizes (Cohen's d with 95% CI) for these changes were: memory composite 0.23 (−1.0– 1.5) for high baseline cortisol, 0.04 (−.9– 1.0) for low; executive function composite 0.68 (−0.7– 1.9) for high baseline cortisol, 0.34 (−0.7– 1.3) for low; PSWQ-A: 0.73 (−0.6– 1.9) for high baseline cortisol, 0.2 (−0.8– 1.2) for low cortisol.

At week 12 (eight weeks after discontinuation of mifepristone), improvements in memory and PSWQ-A appeared to persist, while improvements in executive function seemed to decline.

Changes in cortisol

Both baseline and week 4 cortisol values are available for 12 participants. These showed a marked increase, with a magnitude to a prior study of mifepristone in older adults (Pomara et al., 2006), by the end of the mifepristone treatment, from 5.4 ng/ml (SD 2.5) to 31.9 ng/ml (SD 17.1); $t = 5.6$, $p < 0.001$). Week 12 cortisol values (after 8 weeks off mifepristone) are only available for 7 participants. By week 12, their cortisol values were back down to approximately the same as baseline (baseline= 6.0 ng/ml [SD 2.7]; week 12= 6.9 ng/ml [SD 3.4]; $t = 0.75$, $p = 0.48$).

Discussion

The study offers the first pilot test of an antiglucocorticoid medication for older adults with anxiety disorders and co-occurring cognitive dysfunction. This treatment development is important because of the aging of the population, the high prevalence of anxiety disorders in older adults, and the common co-occurrence of cognitive dysfunction (Lenze and Wetherell, 2011). New treatments that target glucocorticoid excess may be able to rescue cognitive impairment and improve anxiety symptoms.

Our two key findings are: first, we found that three-four weeks of mifepristone 300 mg/day was feasible, safe, and generally well-tolerated in a group of older adults. Second, we observed that people with high cortisol at baseline showed improvements in memory, executive function and reduced severity of worry. We did not find these improvements in people with low to normal cortisol.

These two findings support the further development of mifepristone, and they generate the concept of antiglucocorticoid medication as a *targeted treatment*: it is likely not appropriate for all older adults with mental disorders and co-occurring cognitive dysfunction, but only those who exhibit glucocorticoid excess. This may comprise a substantial proportion of older adults across a range of phenotypic expressions of anxiety, depression, and other high

stress states (Veen et al., 2011, Vasiliadis et al., 2013) based on recent research in late-life anxiety disorders and older studies in depression (Mantella et al., 2008) (Sharma et al., 1988, Chaudieu et al., 2008). Many such individuals may have very mild or prodromal Alzheimer's Disease or other since degenerative disorders which have a long prodromal phase and induce stress-independent effects on the HPA axis (Pomara et al., 2006). Memory recall in these patients has also been previously reported to improve in response to mifepristone (Pomara et al., 2002), additively or independent of stress-related effects.

A third observation from this study is that memory improvements and worry reduction appeared to persist after the discontinuation of mifepristone (although we did not find this with executive improvements). In particular, persistent worry reduction eight weeks after stopping mifepristone stands in marked contrast to the high relapse rate that is seen in late-life anxiety disorder when traditional pharmacotherapy (i.e., SSRI) is withdrawn (Wetherell et al., 2013). This persistent of effect is consistent with the findings in a preclinical model (Hu et al., 2012) which found that the negative effect of glucocorticoids on neurogenesis could be reset by a single infusion of mifepristone. On the other hand, we found that cortisol levels eight weeks after the discontinuation of mifepristone had returned to their baseline (i.e., high) levels; in other words we did not find a persistent change in HPA axis activity. This findings differ from a previous study in young adults with bipolar disorder and schizophrenia which found blunting of HPA activity two weeks after mifepristone cessation (Gallagher et al., 2008). Whether this finding suggests that mifepristone's benefits (if indeed it is beneficial) start to "wear off" around eight weeks post-discontinuation would require a longer follow-up.

Next steps in this research

Clinical development of mifepristone or any antiglucocorticoid therapy must address many unknowns, as is typical with any novel mechanism agent (Macaluso et al., 2011). What are the optimal dose and duration of treatment? Does the treatment need to be chronic, or do its benefits persist after it is discontinued (and if so, for how long)? What is the phenotype of those most likely to benefit (i.e., how best to identify individuals who suffer from glucocorticoid excess and its brain/cognitive consequences)? Finally, what is the clinical picture of improvement (what symptomatic, cognitive, and/or functional changes) and how are these best measured? All of these questions must be answered prior to moving to large RCTs to establish efficacy.

To answer the above questions, it is argued that one or more "learn and confirm" cycles are needed (Sheiner, 1997), consisting of small trials in humans with a focus on the treatment's effect on pathophysiology (Paul et al., 2010). In the case of mifepristone, such mechanistic research can be informed by our understanding of its pathophysiology from preclinical models (Joels, 2011, Matrisciano et al., 2011, Hu et al., 2012), as well as prior clinical trials of mifepristone in other neuropsychiatric conditions (Sartor and Figg, 1996, Heikinheimo and Kekkonen, 1993, Heikinheimo, 1997) (Lamberts et al., 1992) (Blasey et al., 2011, Nelson, 2012) (Belanoff et al., 2002, Gallagher et al., 2005, Golier et al., 2012, Watson et al., 2012, Young et al., 2004a, Pomara et al., 2006). For example, because research in psychotic depression has suggested that high plasma levels of mifepristone are needed for

clinical benefit (Blasey et al., 2011), future research should examine not only dose but level of mifepristone as a predictor of response. Safety, as well, will depend on dose, as well as duration of the treatment, since little long-term data exist on its safety (Fleseriu et al., 2012). As already seen in this small case series, biomarker findings, rather than loyalty to DSM diagnosis, is likely to be the defining feature of the targeted population. Neuroimaging and other (e.g., HPA axis) markers will need to address the underlying pathophysiology (Andreescu et al., 2013), and will need high test-retest reliability (Borsook et al., 2013). On the positive side, such research could rationally develop new treatments while also answering fundamental clinical translational questions about the pathophysiology of stress and aging.

In summary, these results are promising for the further development and testing of mifepristone, and other medications that ameliorate glucocorticoid excess, for older adults with anxiety disorders and co-occurring cognitive dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

1. We tested a 3–4 week course of mifepristone 300mg daily for older adults with anxiety and co-occurring cognitive dysfunction.
2. In this treatment development study, our key findings are (a) evidence for the feasibility of mifepristone in this population, including safety, tolerability, acceptability, (b) in those with baseline high cortisol levels, mifepristone was associated with improvements in memory, executive function, and worry symptoms. The memory and worry improvements appeared to persist, 8 weeks after the discontinuation of mifepristone.
3. These preliminary findings suggest that antiglucocorticoid therapy may be a mechanistic and targeted treatment to develop in older adults with evidence of glucocorticoid excess and its cognitive and emotional sequelae.

Memory

Executive function

Worry severity

Figure 1. Changes in memory, executive functioning, and worry severity with mifepristone
The sample was divided into two groups: those with baseline peak cortisol > 6 (solid line, $n=5$) and those with cortisol < 6 (dashed line, $n=8$). For memory and executive function, we used a composite z-score of all of the relevant tests done (e.g., for memory z-score, both immediate and paragraph recall for list and paragraph learning).