NATIONAL REGISTER OF HEALTH SERVICE PSYCHOLOGISTS

CLINICAL WEBINARS

FOR HEALTH SERVICE PSYCHOLOGISTS

TRANSLATING RESEARCH TO PRACTICE

Combined Treatments for Depression: Evidence and Interventions

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Executive Officer of the National Register of Health Service Psychologists

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National Register of Health Service Psychologists

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Dr. Morgan Sammons is the Executive Officer of the National Register of Health Service Psychologists. Dr. Sammons is a retired Captain in the US Navy, where he served as Specialty Leader for Navy Clinical Psychology and as a special assistant to the US Navy Surgeon General for mental health and traumatic brain injury. Dr. Sammons was one of the first prescribing psychologists in the nation, having begun the Psychopharmacology Demonstration Project in 1991. Dr. Sammons is board certified in clinical psychology and a Fellow of the American Psychological Association.

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- No conflicts of interest to report
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References/Citations

- Qaseem, A., et al. (2016). Nonpharmacologic versus pharmacologic treatment of adult patients with MDD…*Annals of Internal Medicine, 164*, 350-359.
- Health Quality Ontario (2017). Psychotherapy for MDD and GAD: A health technology assessment. *Ontario Health Technology Assessment Series, 17*, 1-67
- Dunlop, et al. (2017). Effects of patient preferences on outcomes in the PReDICT study. *American Journal of Psychiatry*, 24 Mar; doi: 10.1176/appi.ajp.2016.16050517
- NICE Guidance: https://www.nice.org.uk/guidance/conditions-and-diseases/mental-health-and-behavioural-conditions/depression

Learning Objectives

- Analyze the research literature surrounding combined treatments for depression.
- Demonstrate evidence-based practices regarding combining pharmacological and nonpharmacological treatments for depression.
- Discuss combining drug and nondrug treatments for depression.

What This Presentation Does NOT Cover

- Indications for specific antidepressants
- Pharmacological augmentation strategies
- Specific psychotherapeutic maneuvers

Use of Antidepressants More Common, Psychotherapy Less

- Olfson and Marcus (2009) data abstracted from Medical Expenditure Panel Survey:
  - 20% of US population has sought MH tx (2003), compared to 12% in early-1990s. Rate of use of ADPs doubled from 13-23M people yearly.
  - Most got Rx, not psychotherapy. Less than 20% of those getting an antidepressant for depression got psychotherapy, compared to 30% a decade ago, but length of psychotherapy remained the same (~8 visits)
  - Rate of use of antipsychotics among depressed pts also increased significantly.
    - Olfson M., & Marcus, S. (2009). National Patterns in Antidepressant Medication Treatment *Archives of General Psychiatry, 66, 848-856.*
- General MEPS data indicate higher use of psychotropics in adults:
  - 16.7% with ≥ 1 Rx for psychotropic
  - 12% using antidepressants
  - 8.3% using sedative hypnotics
  - 1.6% using antipsychotics
    - Morrison, T. J., & Mattison, D. R., (2017) Adult Utilization of Psychiatric Drugs…*Annals of Internal Medicine, 177,* 274-275. doi: 10.1001/jamainternmed.2016.7507.

Combined Treatments

Evidence and Guidelines

American College of Physicians Guideline on Depression (2016)

- Somewhat surprisingly, ACP guideline recommended *either* an Second Generation Antidepressant (SGA) or CBT for adult depression.
- SGAs = SRIs, SNRIs, bupropion (Wellbutrin), mirtazapine (Remeron), nefazone (Serzone, no longer commonly available), trazodone (Desyrel).
- In general, low quality evidence for combined interventions, with exceptions:
  - Increased functional capacity: SGA + CBT > SGA
  - Increased remission: SGA + IT >SGA

Qaseem, A., et al. (2016). Nonpharmacologic versus pharmacologic treatment of adult patients with MDD…*Annals of Internal Medicine, 164*, 350-359.

NICE Guidance for Depression (April 2018)

Subthreshold or mild depression:

- Guided self-help based on CBT
- Computerized CBT protocols
- Structured group physical activity
- Avoid pharmacotherapy unless subthreshold depression present for > 2 years

Moderate to severe depression:

- High intensity psychotherapy (CBT or IPT) + pharmacotherapy
- Maintain pharmacotherapy for 6 months post remission
- High risk of relapse:
  - Individual CBT
  - Mindfulness based cognitive therapy

NICE Guidance: https://www.nice.org.uk/guidance/conditions-and-diseases/mental-health-and-behavioural-conditions/depression

Ontario Health Technology Assessment of Psychotherapy for MDD and GAD

- 2016 meta-analytic review of interventions for MDD and GAD undertaken for province of Ontario.
- Looked at individual or group interventions vs. TAU for patients aged 18-75.
- Broadly, IPT or CBT found to reduce severity, improve recovery odds, and improve QALY (Quality Adjusted Life Year) scores.
- Structured group therapy provided by nonphysicians was deemed most cost-effective.

Health Quality Ontario (2017). Psychotherapy for MDD and GAD: A health technology assessment. *Ontario Health Technology Assessment Series, 17*, 1-67.

Key Points from the Ontario HTA (for depression):

- Treatment with CBT, interpersonal therapy, or supportive therapy reduces symptoms of major depressive disorder and increases response/recovery posttreatment
- CBT and interpersonal therapy significantly reduce the risk of relapse/recurrence of major depressive disorder
- Individual CBT significantly improves posttreatment recovery from major depressive disorder compared with group CBT
- Combined therapy (CBT with pharmacotherapy) significantly improves treatment response compared with pharmacotherapy only
- CBT significantly improves treatment response compared with pharmacotherapy only following termination of both acute interventions

PReDICT Studies

- Emory Predictors of Remission to Individual and Combined Treatments (PReDICT) study. Protocol published 2012, examined biological, psychological contributors to moderate depression and outcomes of treatment:
  - Randomized 306 previously untreated patients to one of three 12 week treatments: CBT, duloxetine (Cymbalta), escitalopram (Lexapro)
  - Assessed 4 factors in depression: Despair, Mood and Interest, Sleep, and Appetite.
  - Conclusions: Rx hastened response on the Despair & Mood/Interest factors, but no other differences, overall outcomes equivalent.
  - Patient preference for type of treatment predicted adherence but not remission.
  - The mean estimated overall decreases in HAM-D score did not significantly differ between treatments (CBT: 10.2, escitalopram: 11.1, duloxetine: 11.2).
  - Remission rates did not significantly differ between treatments (CBT: 41.9%, escitalopram: 46.7%, duloxetine: 54.7%).

Dunlop, et al., (2017). Effects of patient preferences on outcomes in the PReDICT study. *American Journal of Psychiatry*, 24 Mar; doi: 10.1176/appi.ajp.2016.16050517

Mounting Evidence for Combined Treatments

- Recent Japanese RCT: Medication v combined Rx + 16 week psychotherapy for treatment resistant depression:
  - 80 pts treated with ≥1 failed treatment of depression
  - 16 weeks of CBT + Rx vs. maintenance Rx only.
  - Combined group more likely to demonstrate response.
  - Response maintained at 12 month follow-up.
    - Nakagawa, et al. (2017). Effectiveness of supplementary CBT for pharmacotherapy resistant depression…*Journal of Clinical Psychiatry*, doi:10.4088/JCP.15m10511
- Large Finnish trial of 1515 pts with MDD randomized to Rx, IPT, or group tx: All improved at 12 mo follow-up (42% IPT, 61% group, 42% Rx; mean 50% reduction in HAM-D scores.
  - Saloheimo, et al (2016). Psychotherapy effectiveness for MDD…*BMC Psychiatry*, 16:131.

And if *Consumer Reports* Says So

- Survey of 1,500 respondents treated for depression, reported in July 2010 issue.
- Psychotherapy as good as meds for most ~50% responded to meds, ~46% to psychotherapy, but combination of Rx and at least 7 talk therapy sessions yielded superior outcomes
- No advantage to using SNRIs over SSRIs (more sexual SEs with SNRIs)

Key Components for Effectively Combining Pharmacotherapy and Psychotherapy

- Initial assessment
- Patient preference
- Informed consent
- Assessing response to medication
- Assessing response to psychotherapy
- Discontinuation of treatment and follow-up

Working with Prescribers: The Therapeutic Triangle

Most prescribers are likely to be primary care physicians or NPs, and not specialists in mental health meds or psychiatrists. Accordingly of key importance to establish a good working relationship with providers.

1. Advise prescribers that you are willing to provide an assessment and treatment recommendations in cases where they contemplate prescribing an antidepressant. In your assessment, include the patient's past medication history, and response to other treatments, if known.
2. Advise prescribers that evidence indicates that *where Rx is indicated*, combined therapy yields better outcomes.
3. Since you will most likely see the patient more frequently than the PCM, establish in advance a mutually convenient communications scheme so you can advise the PCM of emergence of side effects, other considerations affecting choice, dose or discontinuation of medication.
    - Particularly at times of predicted high intensity of care or anticipated dose changes: Starting a medication and choosing to discontinue medication.

Informed Consent Essentials

- Type of treatment:
  - Pharmacological
  - Psychological
- Patient preference is key:
  - Outcomes roughly equivalent: Often, initial response is more rapid using pharmacology, long term benefits more lasting with psychotherapy.
  - Goal: For first onset, remission. For relapsing, response.
- Treatment plan must address:
  - Identified symptoms
  - Psychosocial stressors
  - Lifestyle considerations (diet, exercise, alcohol intake)

Informed Consent

- Indications for pharmacotherapy:
  - Severely depressed mood, persistent anhedonia, physical symptoms (anergia, malaise, appetite suppression, prior depressive episodes, prolonged dysthymia)
- Indications for psychotherapy:
  - Suicidal thinking
  - Social withdrawal/interpersonal dysfunction
  - Psychosocial stressors
  - Self-defeating cognitions
- Risks, benefits, side effects of medication
  - Alternatives must include “no treatment”
  - Discuss initiation, continuation, and discontinuation side effects.
- Duration of treatment:
  - Agreed upon endpoints
  - Response vs. remission

Informed Consent (Continued)

- **If the patient chooses pharmacotherapy**
  Informed consent must address: Risks, benefits, common side effects (including initiation and discontinuation side effects), costs, interactions with other medications/diet/alcohol; toxicity and lethality, therapeutic endpoints (response vs. remission).
- **If the patient chooses psychotherapy**
  Informed consent must address: Risks, benefits and alternative treatments (including no treatment) associated with choice of therapy, time to response, cost, duration of treatment, therapeutic endpoints (response vs. remission).

Evidence Supports Most Active, Planful Psychotherapies for Depression

CBT:

- Most studied.
- Easily manualized.
- Most likely to address dysfunctional cognitive schemae and behavioral manifestations of depression.
- Numerous variants: Group CBT, mindfulness based CBT approaches.

IPT

- Substantial body of evidence supports.
- Major focus on interpersonal aspects of depression.

Assessment: Research Rating Scales May Assist Diagnosis, Outcomes Measures of Limited Clinical Utility

Initial Assessment*

- MADRS
- HAM-D
- PHQ 9
- Beck Depression Inventory

*Recall that snapshot tools do not render diagnostic clarity: A careful history does.

Throughout the treatment course

- Informed consent: Identify and incorporate target symptoms into the treatment plan.
- Hopelessness/despair/suicidal ideation
- Specific psychomotor deficits (low energy, lack of appetite)
- Mood and interest (inc. social engagement)
- Sleep
- Affective reactivity

Gauging Treatment Response in the Clinic: Difficulty in Distinguishing Response Complicates Assessment

Symptoms responsive primarily to medication

- Affective reactivity
- Sleep
- Circadian rhythm disruption
- Appetite
- Low energy

Symptoms responsive to psychotherapy

- Despair/hopelessness
- Negative ruminations
- Self-deprecatory thoughts
- Cognitive schemae: Attributional errors

Combined Treatment Phase Intensity (all time periods approximate)

- Initiation of pharmacotherapy:
  - Start at low dose for 3-7 days
  - Monitor for common initiation side effects
    - Insomnia
    - Nausea, diarrhea, GI upset
    - Irritability and increased anxiety
    - Akathisia
    - Suicidal ideation
  - 5-14 days: If low intensity or well-managed, increase dose to therapeutic level, or per standard dose increase.
- Frequency (2-3 times weekly or prn, in person, email, phone): Assessment of severe initiation symptoms, reassurance, discontinuation as needed, additional pharmacology as needed.
- Continuation phase (1-6 months)
  - Monitor for side effects, continue patient education:
    - Weight gain
    - Loss of libido/sexual functioning
    - Responsiveness of target symptoms
    - Dose titration
    - Standard psychotherapy regimen
- Discontinuation and maintenance phase (6-12 months)
  - Structured dose reduction scheme: half-doses for 2-3 weeks, then further titrate or stop:
  - Informed consent: Recurrent symptoms v. discontinuation side effects (irritability, insomnia, affective reactivity, suicidal ideation).
  - Increased patient contact to monitor for recurrence of depression.

Combined Treatment: Psychological Interventions

- Assessment and early intervention (1-2 weeks):
  - Diagnostic workup and informed consent
  - Identification of psychosocial issues
  - Mutually established treatment goals for pharmacotherapy and psychotherapy
  - Establishment of lifestyle goals
- Frequency: 1-2x weekly, phone or email prn.
- Maintenance phase:
  - At least 3-4 months of individual and or group treatment
- Frequency: Weekly, increase intensity at time of medication discontinuation.
- Continuation phase: 3-12 months
- Frequency: Individual psychotherapy reduce to biweekly and later monthly, group psychotherapy may assist weekly or biweekly, monitor psychosocial engagement prn.

Q&A

- Andrew Boucher will read select questions that were submitted via the Q&A feature throughout the presentation.
- Due to time constraints, we will not be able to address every question asked.

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Thank You for Joining Us!

- If you have comments or feedback regarding this webinar, please email CESupport@nationalregister.org
- We hope you can attend our next webinar on Sept 12: Self Care with Dr. John Norcross.

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Serotonin Reuptake Inhibitors (SRIs or SSRIs)

SRIs: Drug (trade)	Generic	Indication	Dose	Concerns, Cautions, Pearls
Prozac	Fluoxetine	MDD, Bipolar I, Bulimia, PD, TRD Children: MDD OCD	10-80 mg/d 10-20 mg/d 10-60 mg/d	Very long half life (may help avoid discontinuation symptoms)
Prozac weekly		MDD, continuation	90 mg	Weekly enteric coated capsule
Sarafem		PMDD	20 mg/d	Continuous or intermittent dose schedule
Viibryd (2011)	Vilazodone	MDD	10-40 mg/d titrated up weekly; max 20 mg with 3A4 inhibitors	5HT1a partial agonist Monitor 3rd trimester exposed neonates for Persistent Pulmonary Hypertension of the Newborn, discontinuation syndrome, 3A4 interactions
Zoloft		Social anxiety, PD OCD MDD, PMDD, PTSD	25-200 mg/d 25-200 mg/d 25-200 mg/d	Adolescents and adults Adults 6 and up Adults

Serotonin Reuptake Inhibitors (SRIs or SSRIs)

SRI (Trade)	Generic	Indications	Dose	Concerns, Cautions, Pearls
Trintillix (2013, 2016)	Vortioxetine	MDD	5 mg/d then 10-20 mg/d	5HT1a agonist 5HT3 antagonist Caution with 2D6 poor metabolisers & coadministration with CYP inducers; Name confusion with Brilinta (ticagelor; platelet inhibitor) FDA approved NAME CHANGE in 2016.
Celexa	Citalopram	Depression	10-40 mg/d	Max dose reduced from 50 to 40 mg due to ECG change (long QT)
Lexapro	Escitalopram	MDD GAD	5-30 mg/d, also as oral solution	5-20 mg/d, age 12 and up 5-10 mg/d
Luvox	Fluvoxamine	OCD	50-300 (adults) 25-200 (peds)	Indicated for OCD only 8-17 years

SRI antidepressants continued: Paroxetine a (not generally recommended for first line treatment)

Paxil Paxil CR Pexeva Brisdelle (2014)	Paroxetine	Paxil Paxil CR Pexeva Brisdelle (2014)	Paroxetine	MDD GAD PTSD OCD PD PMDD	20-50 mg/d 20 mg target dose 20-40 mg 40 mg target 40 mg target 7.5 mg only	Very sedating, best given at night, note 1st trimester cardiac defect risk, unusual discontinuation symptoms. Max dose 60 mg/d. Equivocal approval process Menopausal hot flashes only

Serotonin, norepinephrine and dopamine reuptake inhibitor (SNDRI) serotonin antagonist and reuptake inhibitor, (SARIs)

Drug (Trade)	Drug (Generic)	Indication	Dose	Action	Concerns, cautions, pearls
Serzone* *unavailable; only as generic	Nefazodone	Depression	100-300 mg twice daily Max 600 mg/d Contraindicated with: Carbamazepine Pimozide Terfenadine Cisapride Astemizole	SNDRI: 5HT, NE, DA, reuptake inhibitor Weak reuptake inhibitor, Agonist at: 5HT1A, 5HT2A, Alpha-1 receptors	Serzone sales in US halted in 2004 due to fatalities associated with acute hepatic failure Generic available Sedation and orthostasis common Potent 3A4 inhibitor
Desyrel	Trazodone	MDD	50-400 mg daily	5HT antagonist and reuptake inhibitor (SARI)	Strongly sedating; mostly used as sleep aid (50-100 mg/d) priapism
Oleptro (2010; withdrawn?)	Trazodone	MDD	Start 75 x2/d, then 150, up to 375 mg/d.		Somnolence, priapism, prolonged QT interval, orthostasis.

Tetracyclic/Noradrenergic and Specific Serotonin Antagonist (NaSSA)

Drug (Trade)	Generic	Indications	Dose	Actions	Concerns, Cautions, Pearls
Remeron Remeron SolTabs (rapid disintegrating sublingual tablets)	Mirtazapine	MDD (18 and up)	15-45 mg/day Soltabs: Same Better at bedtime	Tetracyclic 5HT1, 5HT2 antagonist Histamine antagonist	Highly sedating (5HT1 antagonism?) MIR may be sexually activating. fMRI studies show enhanced sexual response vs. SRIs.
					SolTabs: Use immediately after removing from blister pack

Serotonin and Norepinephrine reuptake inhibitors (SNRIs)

SNRI: Drug (Trade)	Generic	Indications	Dose	Cautions, Concerns, Pearls
Cymbalta (2004)	Duloxetine	MDD, GAD diabetic neuropathy, fibromyalgia, chronic musculoskeletal pain	40-60 mg/d, max 120 (7 yrs & up) 30-60 mg/d	Lower dose for pain conditions
Effexor Effexor ER Khedezla Pristiq	Venlafaxine	MDD MDD, GAD, PD, Soc. Anx. MDD MDD	75-225 mg/d Max 225 mg/d 50-100 mg/d 50/100 mg/d	Nausea, BP elev. BP caution Khedezla: "No benefit > 50 mg/d" Pristiq: "No benefit > 50 mg/d"
Fetzima (2013)	Levomilnacipran	MDD	40-120 mg/d	3A4 interactions (Note: related molecule, milnacipran (Savella) indicated only for fibromyalgia.

Aminoketone

Drug (trade)	Drug (generic)	Indication	Dose	Cautions, Concerns, Pearls
Wellbutrin Forfivo XL Zyban	Bupropion	MDD Smoking Cessation	200-450 mg/d 150-300 mg/d	Insomnia, CX seizure disorders; morning dosing
Aplenzin (2008)	Bupropion ER	MDD; SAD	174 mg to 348 daily;	Dose = 150-300 mg bupropion; CX seizure disorders

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