항우울제의 작용기전과 부작용

나 해 리
보바스기념병원

안전성
효능
복용의 간편성
가격
삭감 가능성

어떤 약제를 선택해야 하는가?

Pharmacotherapy

- Accurate diagnosis is crucial
  - Different treatment regimen between Unipolar depression (MDD) & Bipolar spectrum disorder
- Objective of Pharmacologic treatment
  - Symptom remission, not just symptom reduction
  - Patient with partial remission
    - Relapse ↑
    - Recurrence ↑
    - Impairment of daily functioning
- The use of Antidepressant(ADT)
  - Significant therapeutic effect: 3-4 weeks later
  - Choice of ADT: Determined by side effect profile – patient's physical status, temperament, lifestyle

Synopsis of Psychiatry 11th edition, 2015

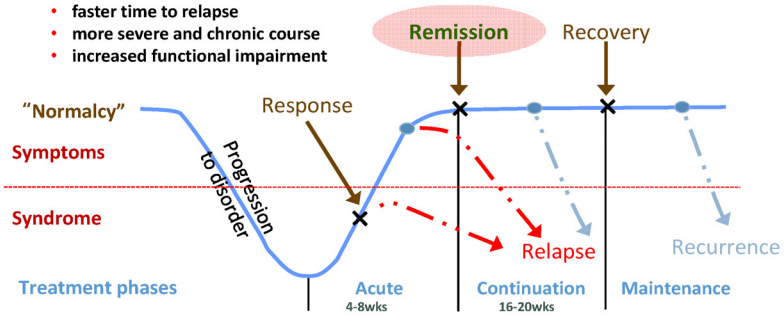
General Clinical Guideline

- Common mistake
  - ➢ Too low a dosage for too short a time
- ADT Dosage
  - ➢ Up to the maximum recommended level
  - ➢ Improvement on a low dosage → Stay → Clinical improvement stop → Raise dosage for a maximal benefit
- ADT Maintenance: at least 4-5 weeks
- ADT Change
  - ➢ No response to appropriate dosage for 2-3 weeks
  - ➢ Can check a plasma concentration for the drug
    - Non-compliance → Education
    - Unusual pharmacokinetic disposition → alternative dosage

Synopsis of Psychiatry 11th edition, 2015

The goal of MDD treatment is Remission!

- ➢ **Residual symptoms and partial response**
  - **increased risk of relapse**
  - **faster time to relapse**
  - **more severe and chronic course**
  - **increased functional impairment**

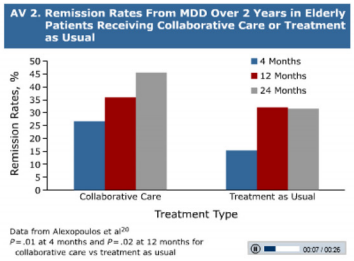


It is clear that many patients do not have a complete response or achieve remission.

Adapted from Kupfer DJ. *J Clin Psychiatry*. 1991;52(suppl 5):28-34.

Remission is the target!

- 60% to 70% respond to treatment;
- Only 30-40% that are optimally treated with first line antidepressants achieve remission (Trivedi 2006, Rush et al 2011)
- **One-third are classified as Treatment resistant depression** (TRD) (Souery et al 2006)
- Residual symptoms are common

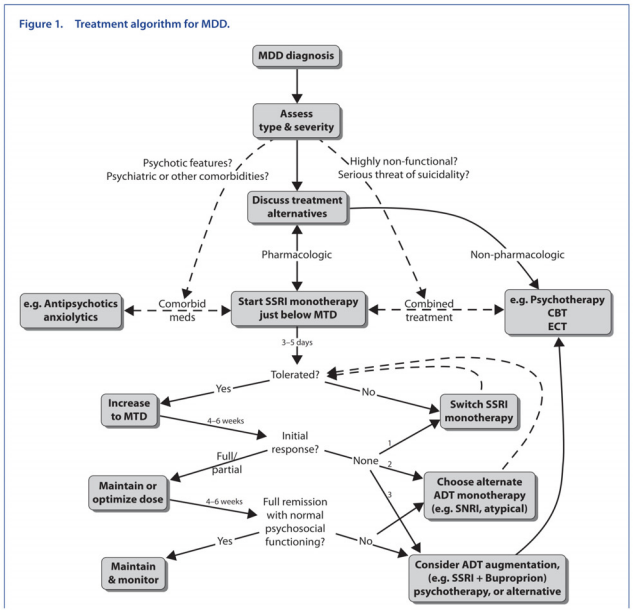


References)
Rush AJ, Kraemer HC, Sackeim HA, et al. Report by the ACNP Task Force on Response and Remission in Major Depressive Disorder. Submitted for publication.
Keller M. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. *JAMA* 2003;289(23):3152-60

Treatment: How long?

- Mild depression:
  - ➢ Antidepressants may not be needed as risk-benefit ratio is poor
- 1st episode (moderate/ severe):
  - ➢ Continue for at least 6-9 months after remission with same dosage
  - ➢ Review needs for continuation of treatment depends on previous seve rity of illness, any residual symptoms or ongoing psychosocial stress
- > 2 episodes in recent past & with functional impairment:
  - ➢ Maintenance treatment at least >2 years
- Some may need lifelong maintenance

Maudsley Guideline11th edition



Drugs Context.
2015 Oct 8;4:212290

우울증의 약물치료의 3단계

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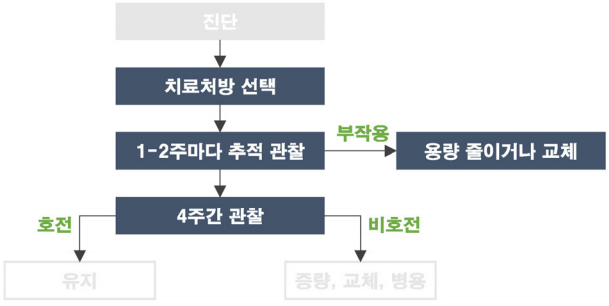
급성기 항우울제 치료



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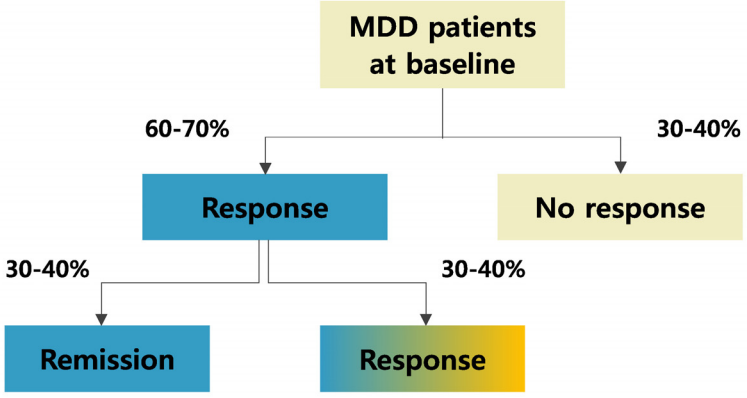
Adapted from WPA/PTD Educational Program on Depressive Disorders

Treatment response: Rule of Thirds



항우울제 처방 시 설명

1. 증상 호소를 충분히 들어준다.
2. 약물 치료가 도움이 될 수 있음을 설명.
3. 우울증은 마음의 병인 동시에 뇌의 생화학적 변화이므로 마음을 잘 다스리면서 뇌의 생화학적 교정 필요.
4. 항우울제는 중독성이 없으며 치매를 일으키지 않음을 지적하여 불안을 경감시킨다.
5. 효과는 2-3주 이후 나타나고 4-6주 지나야 충분한 효과.

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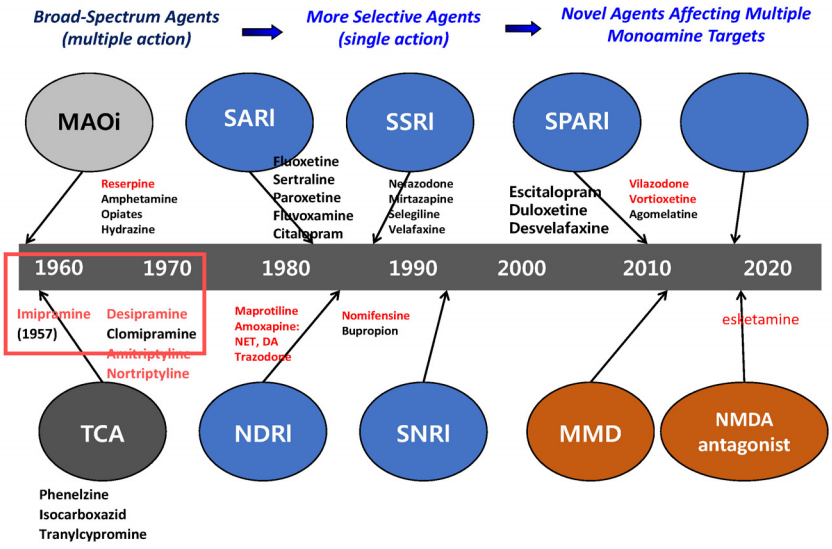
The Evolution of Antidepressants



New Generation Antidepressants

- **Fluoxetine** (Prozac) **1988**
- Bupropion (Wellbutrin IR) 1989
- Sertraline (Zoloft) 1992
- Paroxetine (Paxil) 1993
- Venlafaxine (Effexor) 1994
- Fluvoxamine (Luvox) 1994
- Nefazodone (Serzone) 1995
- Mirtazapine (Remeron) 1996
- **Citalopram** (Celexa) 1998
- Escitalopram (Lexapro) 2003
- Duloxetine (Cymbalta) 2004
- Selegiline transdermal (Emsam) 2006
- Desvenlafaxine (Pristiq) **2008**
- **Milnacipran (Savella, Ixel) 2009**
- **Vortioxetine (Brintellix) 2013**
- **Agomelatine (Valdoxan) 2009**

New Approvals by FDA

- **Vortioxetine**

  Brintellix 9-30 2013 by Takeda & Lundbeck

  Name change to **Trintellix** 5-2-2016

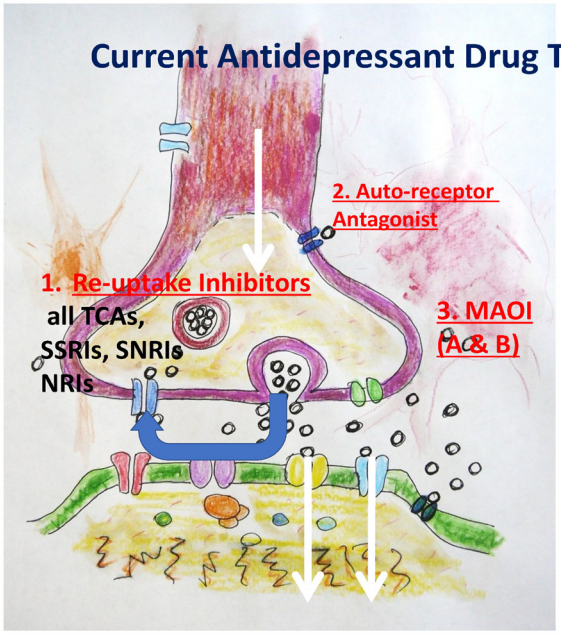
  because of name confusion w Brilinta –anti blood clotting agent
- **Vilazodone** (Viibryd) – January 2011. SSRI w dual action, potentially for depression + (anxiety)
- **Levomilnacipran** (Fetzima)–July 2013 NSRI by Forest .

  Approved for MDD & peripheral neuropathy in US

  and MDD & fibromyalgia in Europe
- Esketamine-March 2019 NMDA antagonist by Janssen.

  Approved for TRD & MDD with imminent risk of suicide in US

Current Antidepressant Drug Targets



Examples:
1. Amitriptyline, Imipramine
Fluoxetine (Prozac)
Paroxetine (Paxil)
Escitalopram (Lexapro)
Venlafaxine
Duloxetine

2. Mirtarzapine, Mianserin

3. Pargyline,
Phenelzine (Nardil)
Selegiline (Deprenyl)
Tranylcypromine (Parnate)
Rasageline

4. Other 5HT receptors

Courtesy by Prof Tang

Antidepressants의 기전 및 종류

Classification		Examples
TCA	Tricyclic Antidepressant	Amitryptiline / Clomipramine/Imipramine / Desipramine / Nortriptyline
MAOI	Monoamine Oxidase Inhibitor	Phenelzine / Isocarboxazid
RIMA	Reversible inhibitor of MAO-A	Moclobemide
SSRI	Serotonin Selective Reuptake Inhibitor	Fluoxetine / Fluvoxamine/Paroxetine / Sertraline / Citalopram / Escitalopram
SARI	Serotonin Antagonist/ Reuptake Inhibitor	Trazodone / Nefazodone
SPARI	Serotonin Partial Agonist/Reuptake Inhibitor	Vilazodone
SNRI	Serotonin Norepinephrine Reuptake Inhibitor	Venlafaxine / Desvenlafaxine / Duloxetine / Milnacipran
NRI	(Selective) Norepinephrine Reuptake Inhibitor	Reboxetine / Evidoxetine / Atomoxetine
NaSSA	Noradrenergic and specific serotonergic antidepressant	Mirtazapine / Mianserin
NDRI	Norepinephrine Dopamine Reuptake Inhibitor	Bupropion
SNDRI	Serotonin-norepinephrine-dopamine reuptake inhibitor	Amitifadine
New ATDs	Melatonergic Antidepressant	Agomelatine
	Serotonin Modulator and Stimulator	Vortioxetine
	NMDA Blockade	Ketamine? Dextromethorphan?

* RED: Approved in Korea, Grey: Unapproved in Korea: Based on KIMS online (2018)

어떤 용량으로, 얼마나 오래?

Medication	Starting dose	Titration, mg/d	Therapeutic Dose	Half-Life	Side Effects	Comments
SSRIs	▪Nausea, dyspepsia, anorexia, tremors, anxiety, sexual dysfunction, jitteriness, insomnia, hyponatremia ▪Risk of serotonin syndrome if combined with certain drugs					
Fluoxetine (Prozac)	10mg once daily	10-20 every 4 weeks	10-60mg once daily	long		
Sertraline (Zoloft)	25mg once daily	50-100 every 2 weeks	50-200mg once daily	short	Loose stool, diarrhea	
Citalopram (Celexa)	10mg once daily	10 every 2 weeks	20-60mg once daily	short		Relative few drug-drug interactions
Escitalopram (Lexapro)	**10mg once daily**	**10 every 2 weeks**	**10-30mg once daily**	**short**		**Relative few drug-drug interactions**
Paroxetine (Paxil)	10mg once daily	10-20 every 2 weeks	20-50mg once daily	short	Dry mouth, drowsiness, fatigue, weight gain hyponatremia	
SNRIs	▪Nausea, sweating, dry mouth, dizziness, agitation, insomnia, somnolence, sexual dysfunction ▪Relative few drug-drug interactions, risk of serotonin syndrome if combined with certain drugs					
Venlafaxine (Effexor)	25mg once daily	37.5-75 every week	25-150 mg twice daily	ultrashort	Hypertension	
Venlafaxine XR (Effexor XR)	37.5mg once daily		75-300mg once daily	short	Hypertension	
Desvenlafaxine (Pristiq)	50mg once daily		50-200mg once daily	short		
Duloxetine (Cymbalta)	30mg once daily	30 at 1-2weeks	20-60mg once daily	short		Should not be broken(enteric coated)

Medication	Starting dose	Titration, mg/d	Therapeutic Dose	Half-Life	Side Effects	Comments
Other newer antidepressants						
Mirtazapine (Remeron)	**15mg every night**	**15 every 1-2weeks**	**15-45mg every night**	**short**	**Sedation, weight gain, no sexual side effects**	**Relative few drug-drug interactions**
Age	75mg once daily	150 at 3-7 days	75-150mg twice or thrice daily	ultrasshort	Insomnia, agitation, jitteriness;no sexual side effects or weight gain	Contraindicated in patients at increased risk for seizures
Bupropion SR (Wellbutrin SR)	100mg once daily		100-150mg twice daily	short	Insomnia, agitation, jitteriness;no sexual side effects or weight gain	Contraindicated in patients at increased risk for seizures
Vortioxetine	**10mg once daily**	**5mg every 2 wks**	**10-20mg once daily**	**long**	**nausea**	**Insufficient data in neurological disorders**
Tricyclic antidepressants	Sedation, weight gain, dry mouth, urinary retention, constipation, blurry vision, orthostatic hypotension, impairment of cardiac conduction					
Nortriptyline (Pamelor)	10mg every night	25 every week	75-125mg every night	short	fatigue	
Desipramine (Norpramin)	25mg once daily	25-50 every week	100-200mg once daily	short	Insomnia, agitation	

Augmentation Agents				
Buspiron	15	15 every week	20-60	60
Lamotrigin	25	25 for 2 weeks, then 50 for 2 weeks, then 100 for 1 week	50-100	200
Liothyronine(T3)	25mcg/d	None	25-50mcg/d	50mcg/d
Lithium	300	150 every 1-2 weeks	600-900	Based on the medication serum level in the individual patient in the context of clinical response and tolerability
Pramipexole	0.375	0.375 every week	0.375-1	1.5
Ropinirole	0.25	0.25 every week	0.25-1.5	2

Basic pharmacokinetics of NAD

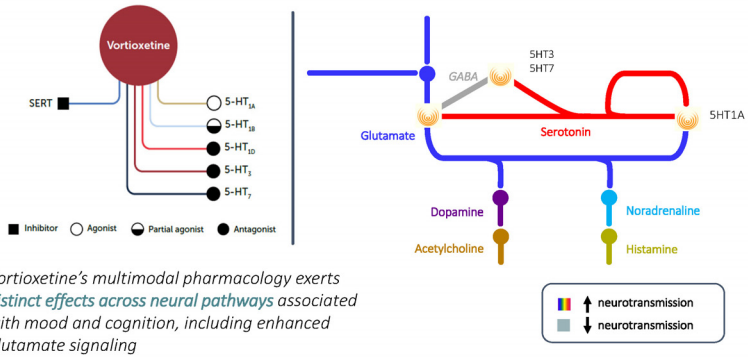
Characteristic	Brintellix®	Pristiq®	Effexor XR®	Cymbalta®	Agomelatine®	Esketamine®
Absorption						
Oral bioavailability	75%	~80%	45%	50%	1%	48%
Half-life ($t_{1/2}$)	~66 hours	~11 hours	5 hours*	12 hours	2-3 hours	7 ~ 12 hours
T_{max}	7-11 hours	~7.5 hours	5.5 hours*	6 hours	1~2 hours	30 min
Coadministration with food	Minimal effects	Minimal effects	Minimal effects	Minimal effects	Minimal effects	Minimal effects
Distribution						
Protein binding	98-99%	~30%	27%*	>90%	95%	43~45%
Metabolism						
Main metabolic route	CYP2D6	Glucuronidation	CYP2D6	CYP2D6, CYP1A2	CYP1A2	CYP2B6, CYP3A4
CYP3A4	Minor metabolic path	Minor metabolic path	Minor metabolic path	Not involved	Not involved	Major metabolic path
CYP2D6	Not involved; minimal inhibition	Not involved; minimal inhibition	Major metabolic path; minimal inhibition	Major metabolic path; moderate inhibition	Not involved	Not involved
Metabolites	3	3	6	>20	hydroxylated and demethylated	Noresketamine
Elimination	<1% unchanged	45% unchanged	5% unchanged	<1% unchanged	<1% unchanged	<1% unchanged

*Values are for venlafaxine (the parent compound)

Vortioxetine (Brintellix®)

- A novel multimodal mechanism of action
- An SSRI + a 5-HT1A full agonist + 5-HT3 receptor antagonist
- Downstream effect of this multimodal action is an increase in **DA, NE, and ACh** activity in the prefrontal cortex (restore some cognitive deficits w depression)
- *High remission rate* (61%) on open label w 10 mg/d
- *Older pts* (age 64 – 88)– 452 pts studied 5 mg/d or placebo. Better in 6 wks w improved cognitions

Vortioxetine (Brintellix®)



Vortioxetine's multimodal pharmacology exerts distinct effects across neural pathways associated with mood and cognition, including enhanced glutamate signaling

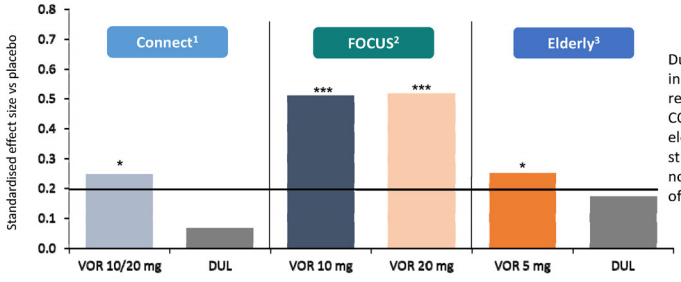
NB. The precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly to humans.

5-HT, serotonin; GABA, gamma-aminobutyric acid; SSRI, selective serotonin reuptake inhibitor; VOR, vortioxetine.

Sanchez et al. *Pharmacol Ther.* 2015 Jan;145:43-57;
Pehrson et al. *CNS Spectr.* 2014 Apr; 19(2): 121–133.

Vortioxetine (Brintellix®)

DSST – Replication: Number of correct symbols, change from baseline at Week 8
(FAS, ANCOVA, LOCF, path analysis; *p<0.05, ***p<0.001)

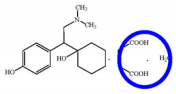


Duloxetine was included as active reference in the CONNECT and elderly studies for study validation, not for comparison of effect sizes.

DSST measures executive functioning, working memory, attention and speed of processing. The effect of vortioxetine on DSST performance is to a large degree independent of the improvement in general depressive symptoms (measured by MADRS / HAMD24)

1. Mahableshwarkar. *Neuropsychopharmacology*. 2015 Jul;40(8):2025-37.
2. McIntyre. *Int J Neuropsychopharmacol*. 2014 Oct;17(10):1557-67.
3. Katona. *Int Clin Psychopharmacol*. 2012 Jul;27(4):215-23.

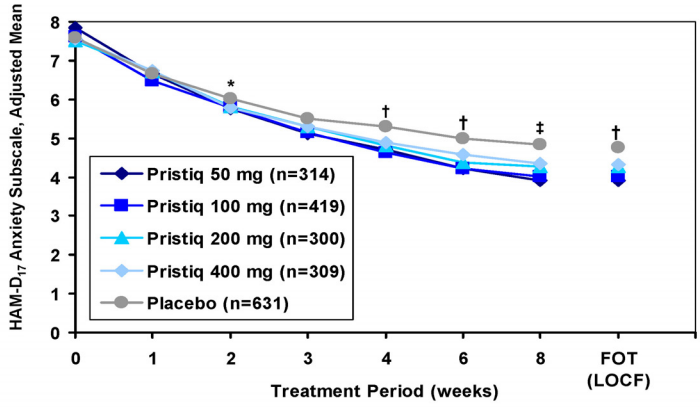
Desvenlafaxine Succinate(Pristiq®)



Succinate salt

- Orally active small molecule
- Selective serotonin/norepinephrine reuptake inhibitor (SNRI)
- Formulated as an extended-release, film coated tablet
- Renal impairment: Clearance decreases
  - ➢ Moderate renal impairment (CrCl 30-50 mL/min) dosing: 50 mg daily
  - ➢ Severe renal impairment and ESRD dosing: 50 mg every other day
  - ➢ Dose should not be escalated in patients with moderate or severe renal impairment or ESRD
- Liver disease: Pharmacokinetic parameters are altered
  - ➢ No adjustment for starting dose is necessary; however, dose escalation above 100 mg/d is not recommended

Improvement in Anxiety Symptoms of MDD With Pristiq®



Data were pooled from 5 randomized, double-blind, placebo-controlled, 8-week studies in MDD assessing the efficacy, safety, and tolerability of Pristiq.
*$P \leq 0.05$ for Pristiq 50 mg/d vs placebo; †$P < 0.05$ for all dose groups vs placebo; ‡$P < 0.01$ for all dose groups vs placebo.
Ahmed S et al. Poster presented at: American Psychiatric Association Annual Meeting. Washington, DC; May 3-8, 2008.
Data on file, Study MDD202_HAMDitem. Wyeth Pharmaceuticals.

Maintenance of the efficacy of PRISTIQ in menopausal vasomotor symptoms

Changes in hot flush (HF) frequency and severity

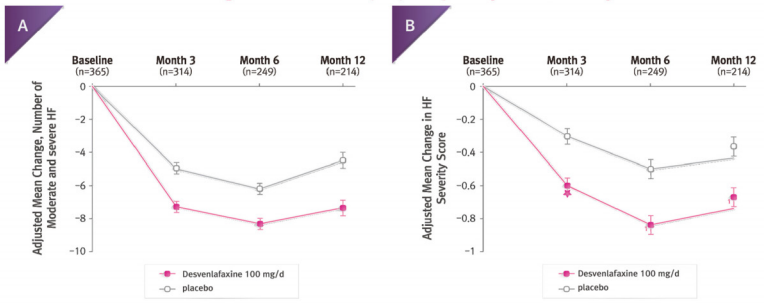


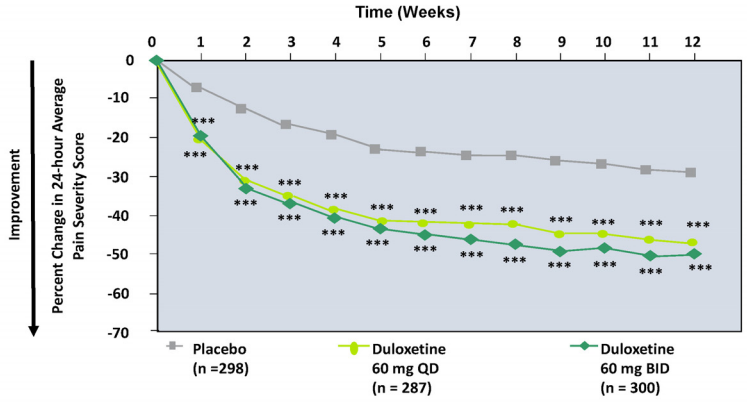
FIG. 2. A: Adjusted mean (SE) change in the number of moderate and severe HFs on months 3,6, and 12 (MITT efficacy substudy population, n=365; observed cases).
B: Adjusted mean (SE) change in the average daily HF severity score on months 3, 6, and 12 (MITT efficacy substudy population, n=365; observed cases).
*P<0.001, desvenlafaxine 100mg/day versus placebo. †P<0.001, desvenlafaxine 100mg/day versus placebo. HF, hot flush; MITT, modified intent to treat (≥1dose of study drug and ≥1 day of baseline and on-therapy HF data).

Pinkerton, Archer, Guico-Pabia, Hwang and Ru-fong (2013)

Duloxetine hydrochloride(Cymbalta®)

- SNRI – Serotonin & NE reuptake inhibitor
- 30mg 28 cap(402 won/cap), 60mg 28 cap(618 won/cap)
- Indications
  - ➢major depressive disorder (MDD)
  - ➢generalized anxiety disorder (GAD)
  - ➢diabetic peripheral neuropathic pain (DPNP)
  - ➢fibromyalgia (FM)
  - ➢management of pain of patients with osteoarthritis (OA) who do not appropriately response to NSAIDs

Duloxetine in DPNP : Pooled 12-week Studies
Change in Average Pain Severity



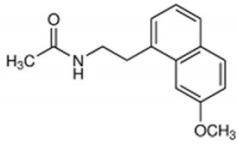
***p≤.001 versus Placebo (MMRM)
Mean baseline score 5.8 out of 10

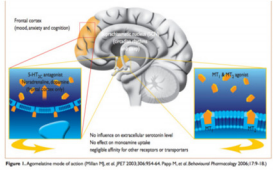
The KFDA approved dose of duloxetine for DPNP is 60mg to 120mg OD.

Fishbain et al. J Pain Symptom Manage 2008;36(6):639-47 MMRM: Mixed-effect Model Repeated Measure

Agomelatine (Valdoxan®, 아고틴®)

VALDOXAN

【약리작용】	멜라토닌 수용체인 MT1, MT2의 선택적 촉진작용과 5-HT2C 수용체 길항작용 두 가지 기전의 시너지 효과로 인해 우울증 환자의 circardian rhythm을 정상화 시키고 항 우울효과를 가짐
【약물구조】	  · 분자식 : C15H17NO2 · 분자량 : 243.3
【약물성상】	진노랑색장방형정제
【적 응 증】	주요 우울증
【용법/용량】	25mg OD(max. 50mg/day)
【부 작 용】	불안, 두통, 어지러움, 졸림, 불면증, 편두통, 흐린 시야, 구역, 설사, 변비, 복부통증, 구토, 다한증, 습진, 가려움증, 요통, 피로, ALAT/ASAT 증가, 체중증가, 체중감소
【주의사항】	신장애, 간손상 위험요인이 있는 환자(비만/ 체중과다/ 비알콜성 지방간, 당뇨, 알콜 과량 섭취), 간손상 위험과 관련된 약물의 병용, 양극성장애/조증/경조증, CYP1A2 저해제와의 병용 투여
【금 기】	본제 과민증, 간장애 환자(즉, 간경화 또는 활성 간 질환) 또는 트랜스아미나제가 정상치의 3배를 초과하는 경우, 강력한 CYP1A2 저해제(예, 플루복사민, 시프로플록사신)와 병용, 갈락토오스 불내성(galactose intolerance), Lapp 유당분해효소결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수 장애(glucose-galactose malabsorption) 환자, 임부, 수유부, 18세 미만의 소아 및 청소년, 75세 이상 고령자, 치매 노인 환자



Esketamine

- S-enantiomer of ketamine (approved in 1970 under NDA 16812 for anesthesia)
- N-methyl-D-asparate (NMDA) receptor antagonist (non-competitive)
- Esketamine already approved in Europe and Latin America for anesthesia indication (IV/IM use)
- Proposed indication: **treatment of TRD** (separate IND also underway for MDD with imminent risk of suicide)
- Route of administration: intranasal (IN)
- Half-life of plasma esketamine: 2-3 hours
- Clinical pharmacology findings:
  - Blood pressure effects last up to 4 hours
  - Sedation and dissociation last up to 4 to 6 hours

Esketamine

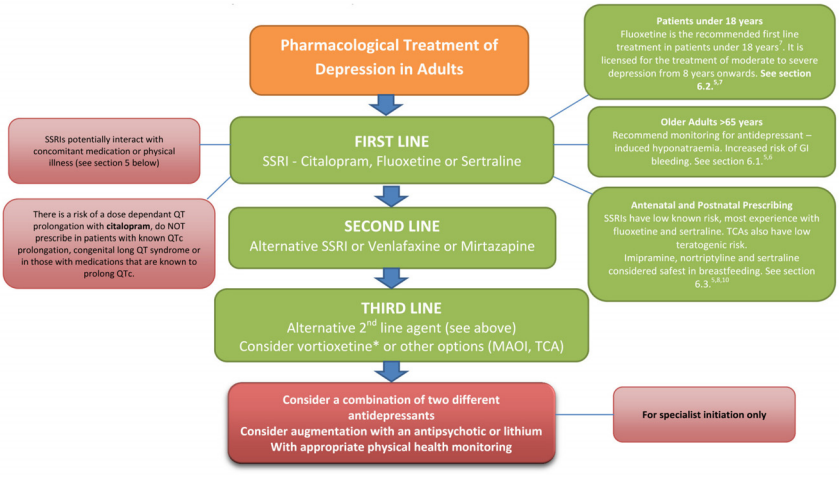
FDA

- IN esketamine given in combination with newly initiated oral antidepressant
- Application:
  - Induction: 56 mg or 84 mg IN esketamine: two times a wk for 4 wks
  - Maintenance: Weekly for next 4 wks ("optimization" per Applicant)
  - Then weekly or every other week depending on treatment response, for ongoing maintenance
- Administration at supervised settings only, with REMS certified clinician
- Main adverse effects identified: Sedation, dissociation, ↑BP , urinary symptoms

Choosing Antidepressants

- All FDA-approved antidepressants are equally effective (~ 50% have a substantial response)
- Considerations in selecting an antidepressant
  - Prior treatment history in patient/family members
  - Patient preferences
  - Expertise of prescribing provider
  - Side effect profile (sedating or activating)
  - Safety in overdose
  - Availability and costs
  - Drug-drug interactions

Recommended Pharmacological Tx for Depression



Guidelines for the Pharmacological Management of Depression: Review date Sept 2018, NICE

Canadian Network for Mood and Anxiety Treatments 2016 Clinical Guidelines for the MDD

Antidepressant (Brand Name(s))	Mechanism	Dose Range
First line (Level 1 Evidence)		
Agomelatine[a] (Valdoxan)	MT_1 and MT_2 agonist; 5-HT_2 antagonist	25-50 mg
Bupropion (Wellbutrin)[b]	NDRI	150-300 mg
Citalopram (Celexa, Cipramil)	SSRI	20-40 mg
Desvenlafaxine (Pristiq)	SNRI	50-100 mg
Duloxetine (Cymbalta)	SNRI	60 mg
Escitalopram (Cipralex, Lexapro)	SSRI	10-20 mg
Fluoxetine (Prozac)	SSRI	20-60 mg
Fluvoxamine (Luvox)	SSRI	100-300 mg
Mianserin[a] (Tolvon)	α_2-Adrenergic agonist; 5-HT_2 antagonist	60-120 mg
Milnacipran[a] (Ixel)	SNRI	100 mg
Mirtazapine (Remeron)[c]	α_2-Adrenergic agonist; 5-HT_2 antagonist	15-45 mg
Paroxetine (Paxil)[d]	SSRI	20-50 mg 25-62.5 mg for CR version
Sertraline (Zoloft)	SSRI	50-200 mg
Venlafaxine (Effexor)[e]	SNRI	75-225 mg
Vortioxetine (Brintellix, Trintellix)[f]	Serotonin reuptake inhibitor; 5-HT_{1A} agonist; 5-HT_{1B} partial agonist; 5-HT_{1D}, 5-HT_{3A}, and 5-HT_7 antagonist	10-20 mg
Second line (Level 1 Evidence)		
Amitriptyline, clomipramine, and others	TCA	Various
Levomilnacipran (Fetzima)[f]	SNRI	40-120 mg
Moclobemide (Manerix)	Reversible inhibitor of MAO-A	300-600 mg
Quetiapine (Seroquel)[e]	Atypical antipsychotic	150-300 mg
Selegiline transdermal[a] (Emsam)	Irreversible MAO-B inhibitor	6-12 mg daily transdermal
Trazodone (Desyrel)	Serotonin reuptake inhibitor; 5-HT_2 antagonist	150-300 mg
Vilazodone (Viibryd)[f]	Serotonin reuptake inhibitor; 5-HT_{1A} partial agonist	20-40 mg (titrate from 10 mg)

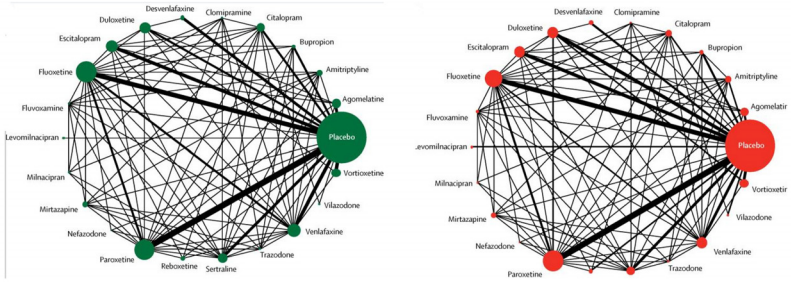
The Canadian Journal of Psychiatry. 2016, Vol. 61(9) 540-560

2016 CANMAT Guideline

* 2016 CANMAT (Canadian Network for Mood and Anxiety Treatment)		
First Line Recommendations		
• SNRIs : Venlafaxine, **Desvenlafaxine**, Duloxetine, Milnacipran		
• SSRIs : Sertraline, Fluoxetine. Citalopram, Paroxetine, Fluvoxamine, Escitalopram		
• Agomelatine, Bupropion, Mianserin, Mirtazapine, or Vortioxetine		
Potential for drug-drug interacions among first-line antidepressants (cytochrome P450 isoenzyme or p-glycoprotein inhibition noted in brackets).		
Minimal or low potential	**Desvenlafaxine** Escitalopram/ Citalopram Mirtazapine Venlafaxine	
Moderate potential	Agomelatine (1A2 substratea) Duloxetine (2D6 inhibitor; 1A2 substratea) Sertraline (2D6 inhibitor) Vortioxetine (2D6 substrate)	Bupropion (2D6 inhibitor) Levomilnacipran (3A4 substrate) Vilazodone (3A4 substrate)
Higher potential	Fluoxetine (2D6, 2C19 inhibitor) Moclobemide (MAO inhibitor precautionsc) Selegiline (MAO inhibitor precautionsc)	Fluvoxamine (1A2, 2C19, 3A4 inhibitor) Paroxetine (2D6 inhibitor)

Comparative efficacy and acceptability of 21 ADTs for the acute treatment of adults with MDD: a systematic review and network meta-analysis

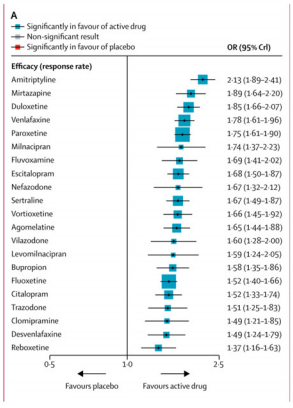
<Network meta-analysis of eligible comparisons for efficacy and acceptability>

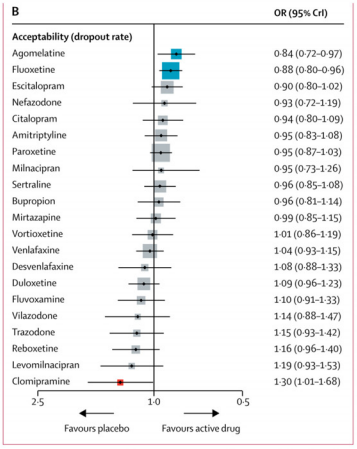


- 522 trials, 116,477 patients and 21 antidepressants were analysed in the acute treatment of adults with major depressive disorder.

Cipriani et al. *Lancet.* 2018 Apr 7;391(10128):1357-1366.

Comparative efficacy and acceptability of 21 ADTs for the acute treatment of adults with MDD: a systematic review and network meta-analysis

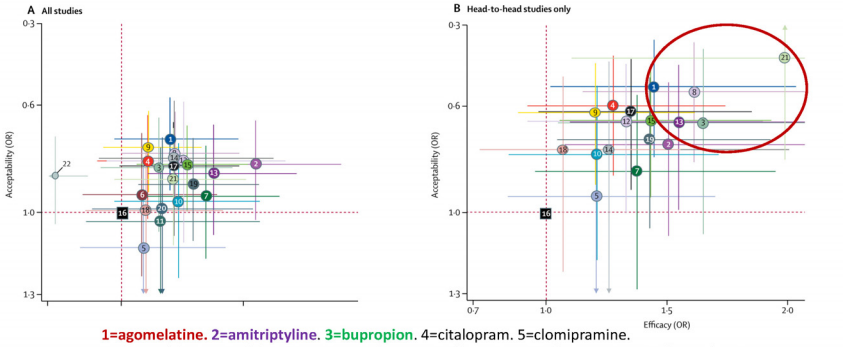




Cipriani et al. *Lancet.* 2018 Apr 7;391(10128):1357-1366.

Comparative efficacy and acceptability of 21 ADTs for the acute treatment of adults with MDD: a systematic review and network meta-analysis

Two-dimensional graphs about efficacy and acceptability



1=agomelatine. 2=amitriptyline. 3=bupropion. 4=citalopram. 5=clomipramine. 6=desvenlafaxine. **7=duloxetine. 8=escitalopram.** 9=fluoxetine. 10=fluvoxamine. 11=levomilnacipran. 12=milnacipran. **13=mirtazapine.** 14=nefazodone. **15=paroxetine.** 16=reboxetine. 17=sertraline. 18=trazodone. **19=venlafaxine.** 20=vilazodone. **21=vortioxetine.** 22=placebo

Cipriani et al. *Lancet.* 2018 Apr 7;391(10128):1357-1366.

항우울제의 선택 I

- 효과성
  - Mirtazapine, duloxetine, venlafaxine>paroxetine, milnacipran, **escitalopram, sertraline**> vortioxetine, agomelatine> bupropion, fluoxetine (Cipriani 2018)
- 수용성 Acceptability
  - Agomelatine, fluoxetine, **escitalopram, sertarline, paroxetine**> milanacipran, bupropion, mirtazapine> venlafaxine, desvenlafaxine, duloxetine
  - (Cipriani 2018)
- 약물 상호작용
  - Escitalopram, sertraline, desvenlafaxine, milnacipran, mirtazapine>> fuloxetine, paroxetine, fluvoxamine

항우울제의 선택 II

- 간질환
  - milnacipran, desvenlafaxine, >> agomelatine, mirtazapine
- 신장질환
  - 대부분 항우울제 가능 >> milnacipran, desvenlafaxine
- 체중증가 필요한 경우
  - Mirtazapine, paroxetine >> bupropion, fluoxetine
- 수면 증진 목적
  - Trazodone 25-50, mirtazapine 7.5, doxepine 3-6, amitriptyline 10-25mg

Weight Change in ATDs

	Weight Change in kg
Paroxetine	2.73
Mirtazapine	2.59
Amitriptyline	2.24
Nortriptyline	1.24
Clomipramine	1.0
Duloxetine	0.71
Escitalopram	0.65
Venlafaxine	0.5
Sertraline	-0.12
Trazodone	-0.2
Fluoxetine	-0.31
Desvenlafaxine	-0.8
Bupropion	-1.87

Chonnam Med J 2018;54:101-112

Effect on sexual functioning

Table 2. Treating MDD while managing SD: Summary of antidepressants and augmentation agents (with lowest effective dose for adults with MDD).

Category A (Improves sexual functioning)	• Sildenafil[2,5*†] • Tadalafil[2,5*†] • Vardenafil[2,5*†] • Flibanserin[26,34,36,37*α] • Bupropion[11,42–44] (100 mg × 2)[74]
Category B (No significant effect on sexual functioning)	• Agomelatine[45–48,75] (25 mg)[65] • Desvenlafaxine[49–51] (50 mg)[51] • Moclobemide[52,53,76] (450 mg)[53] • Trazodone[54–58] (150 mg)[77] • Vilazodone[11,59,60,78] (20 mg)[79] • Vortioxetine[11,61,62,80] (20 mg)[81]
Category C (Significant negative effect on sexual functioning)	• Citalopram[14,42] (20 mg)[82] • Clomipramine[11,33] (100 mg)[83] • Escitalopram[13,14,42,84] (10 mg)[85] • Fluoxetine[14,42] (10 mg)[86] • Imipramine[14,33] (50 mg)[87] • Paroxetine[14,42,84] (20 mg)[88] • Phenelzine[14] (15 mg)[89] • Sertraline[14,43] (50 mg)[90] • Venlafaxine[14,46] (75 mg)[49]
Category D (Inconclusive)	• Duloxetine[13,91,92] (60 mg)[93] • Levomilnacipram[64,65] (40 mg)[65] • Mirtazapine[68–71,94] (15 mg)[95]

*Not an antidepressant.
†Recommended for use with male patients only.
αPrescribed for premenopausal female patients only; not directed to treat SD due to depression or antidepressants.
MDD, major depressive disorder; SD, sexual dysfunction.

1.PR Chokka and JR Hankey, Assessment and management of sexual dysfunction in the context of depression. *Ther Adv Psychopharmacol* 2018, Vol. 8(1) 13–23

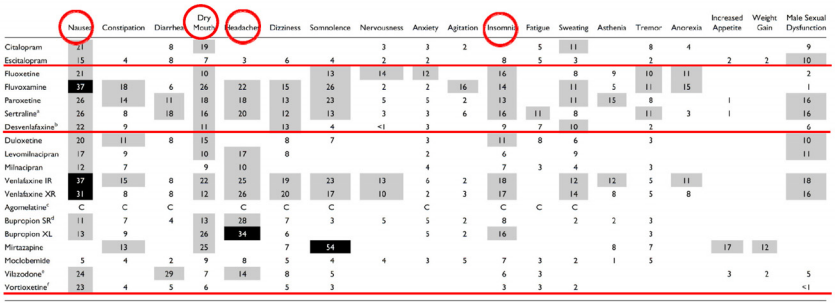
TABLE 2. Antidepressants and Hepatotoxicity

Agents	Gahr (2015)[48]		Montastruc (2014)[49]							
			Spain		France		Italy		Portugal	
	Cases (%)	ROR (95%CI)	Cases (%)	ROR (95%CI)	Cases (%)	ROR (95%CI)	Cases (%)	ROR (95%CI)	Cases (%)	ROR (95%CI)
Agomelatine	334 (19.0%)	6.4 (5.7-7.2)	9 (12.0)	4.9 (2.4-9.7)	22 (16.7)	2.4 (1.5-3.7)	31 (16.1)	5.1 (1.7-4.1)	1 (3.2)	0.9 (0.1-6.4)
Amitriptyline	857 (5.2%)	1.5 (1.4-1.6)	NA	NA	NA	NA	NA	NA	NA	NA
Bupropion	591 (1.2%)	0.3 (0.3-0.4)	6 (0.8)	0.3 (0.1-0.7)	NA	NA	NA	NA	1 (2.1)	0.6 (0.1-4.2)
Citalopram	797 (3.2%)	0.9 (0.8-0.10)	27 (3.9)	1.4 (1.0-2.1)	201 (9.2)	1.2 (1.1-1.4)	10 (3.4)	1.0 (0.5-1.8)	0 (0.0)	-
Clomipramine	608 (7.2%)	2.3 (2.1-2.5)	NA	NA	NA	NA	NA	NA	NA	NA
Duloxetine	2341 (9.0%)	2.7 (2.6-2.8)	10 (2.2)	0.8 (0.4-1.5)	48 (11.4)	1.5 (1.1-2.0)	5 (1.7)	0.5 (0.2-1.2)	2 (3.5)	0.9 (0.2-3.9)
Escitalopram	379 (2.7%)	0.8 (0.7-0.8)	18 (2.8)	1.0 (0.6-1.6)	75 (9.1)	1.2 (0.9-1.5)	6 (2.8)	0.8 (0.3-1.8)	9 (5.5)	1.5 (0.8-3.0)
Fluoxetine	1854 (3.0%)	0.8 (0.8-0.9)	36 (2.5)	0.9 (0.6-1.6)	388 (12.2)	1.6 (1.5-1.8)	6 (2.6)	0.7 (0.3-1.6)	5 (2.2)	0.6 (0.2-1.4)
Fluvoxamine	297 (3.4%)	1.0 (0.9-1.1)	3 (1.3)	0.5 (0.2-1.5)	98 (13.1)	1.8 (1.4-2.2)	NA	NA	0 (0.0)	-
Milnacipran	74 (2.6%)	0.7 (0.6-0.9)	8 (3.6)	1.3 (0.6-2.7)	345 (19.9)	2.9 (2.6-3.3)	4 (16.0)	5.1 (1.5-5.6)	1 (4.6)	1.3 (0.2-9.3)
Mirtazapine	778 (5.2%)	1.5 (1.4-1.6)	23 (3.6)	1.3 (0.8-1.9)	75 (11.8)	1.6 (1.2-2.0)	4 (3.6)	1.0 (0.3-2.8)	1 (2.0)	0.5 (0.0-3.9)
Nefazodone	930 (10.6%)	3.2 (3.0-3.5)	4 (10.8)	4.3 (1.5-12.1)	NA	NA	NA	NA	NA	NA
Paroxetine	1306 (2.2%)	0.6 (0.6-0.7)	41 (2.8)	1.0 (0.8-1.4)	331 (10.1)	1.3 (1.2-1.5)	14 (2.8)	0.8 (0.3-1.8)	4 (1.8)	0.5 (0.2-1.3)
Sertraline	1398 (2.9%)	0.8 (0.8-0.9)	35 (4.5)	1.7 (1.2-2.4)	99 (9.3)	1.2 (1.0-1.5)	11 (3.1)	0.9 (0.4-1.6)	7 (4.1)	1.1 (0.5-2.4)
Tianeptine	124 (13.9%)	4.4 (3.6-5.3)	NA	NA	140 (16.1)	2.3 (1.9-2.7)	NA	NA	NA	NA
Trazodone	386 (3.6%)	1.0 (0.9-1.1)	16 (4.8)	1.8 (1.1-3.0)	NA	NA	1 (1.2)	0.3 (0.0-2.1)	6 (3.5)	1.0 (0.4-2.2)
Venlafaxine	1297 (3.2%)	0.9 (0.86-1.0)	18 (2.5)	0.9 (0.6-1.5)	223 (12.4)	1.7 (1.5-1.9)	7 (2.1)	0.6 (0.3-.1.2)	2 (1.4)	0.4 (0.1-1.5)

[1]based on 9,383,954 adverse drug reactions reports in VigiBase™. ROR: reporting odds ratio. Spain: adverse drug reactions recorded between January 1, 1990, and December 31, 2011, France: ADRs recorded between January 1, 1985, and January 23, 2012, Italy: ADRs recorded between January 1, 2001, and December 31, 2011, Portugal: ADRs recorded between January 1, 1992, and November 8, 2012.

Chonnam Med J 2018;54:101-112

Prevalence of Adverse Events among Newer Antidepressants: Unadjusted Frequency (%)



	Nausea	Constipation	Diarrhea	Dry Mouth	Headache	Dizziness	Somnolence	Nervousness	Anxiety	Agitation	Insomnia	Fatigue	Sweating	Asthenia	Tremor	Anorexia	Increased Appetite	Weight Gain	Male Sexual Dysfunction
Citalopram	21		8	19				3	3	2		5	11		8	4			9
Escitalopram	15	4	8	7	3	6	4	2	2		8	5	3		2		2	2	10
Fluoxetine	21			10			13	14	12		16		8	9	10	11			2
Fluvoxamine	37	18	6	26	22	15	26	2	2	16	14		11	5	11	15			1
Paroxetine	26	14	11	18	18	13	23	5	5	2	13		11	15	8		1		16
Sertraline[a]	26	8	18	16	20	12	13	3	3	6	16	11	8		11	3	1		16
Desvenlafaxine[b]	22	9		11		13	4	<1	3		9	7	10		2				6
Duloxetine	20	11	8	15		8	7		3		11	8	6		3				10
Levomilnacipran	17	9		10	17	8			2		6		9						11
Milnacipran	12	7		9	10				4		7	3	4		3				
Venlafaxine IR	37	15	8	22	25	19	23	13	6	2	18		12	12	5	11			18
Venlafaxine XR	31	8	8	12	26	20	17	10	2	3	17		14	8	5	8			16
Agomelatine[c]	C	C	C		C	C	C		C		C	C	C						
Bupropion SR[d]	11	7	4	13	28	7	3	5	5	2	8		2	2	3				
Bupropion XL	13	9		26	34	6			5	2	16				3				
Mirtazapine		13		25		7	54							8	7		17	12	
Moclobemide	5	4	2	9	8	5	4	4	3	5	7	3	2	1	5				
Vilazodone[e]	24		29	7	14	8	5				6	3					3	2	5
Vortioxetine[f]	23	4	5	6		5	3				3	3	2						<1

The Canadian Journal of Psychiatry. 2016, Vol. 61(9) 540-560

Clinical Correlates of Enhanced Neurotransmission

Serotonergic side effects

- GI upset
- Sexual dysfunction
- Sleep disturbance
- *With long-term use*
  - ✓ Weight gain
  - ✓ Suppression of dopamine neurotransmission may lead to:
    - ➢ Decrease in ability to experience pleasure
    - ➢ Apathy and decreased motivation
    - ➢ Decreased attention and cognitive slowing

Noradrenergic side effects

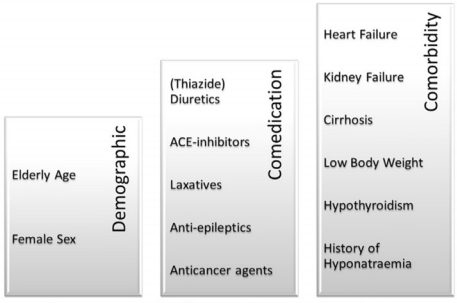
- Tremor
- Tachycardia

Dopaminergic side effects

- Psychomotor activation
- Aggravation of psychosis

Stahl SM. Essential Psychopharmacology
Richelson E., Pharmacology of antidepressants, Mayo Clin Proc, 1994
Kapur, Serotonin-dopamine interaction and its relevance to schizophrenia, Am J Psychiatry, 1996

Antidepressants and the Risk of Hyponatremia: A Class-by-Class Review of Literature



	SSRI	Venlafaxine	TCA	Mirtazapine	Duloxetine	Bupropion	MAOI	Reboxetine
Number of studies and case reports	15 > 90 CR	6 9 CR	3 21 CR	2 7 CR	1 12 CR	0 4 CR	0 3 CR	0 2 CR
Incidence	0.06–40%	0.08–71%	0.005%–16.7%	0%–0.004%	0.11%	–	–	–
OR	1.5–21.6	–	1.0–4.9	–	–	–	–	–
Risk group	{Higher risk}		{Moderate risk}			{Insufficient evidence}		

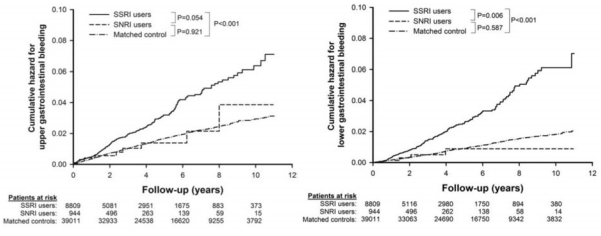
Note: Some case reports involve more than 1 case; all cases are counted separately in this table.
CR = case report; OR = odds ratio.

- Hyponatremia is a potentially dangerous S/E of ADDs and is not exclusive to SSRIs.
- A relatively higher risk of hyponatremia with SSRIs and venlafaxine, especially when combined c risk factors.
- Mechanism-the hypothesis of a serotonin-induced increase in ADH, mediated by hypothalamic serotonin receptors.

Psychosomatics 2014:55:536–547

SSRI, But Not SNRI, Increased Upper/Lower GIB

- After adjusting for age, sex, presence of HTN, DM, CAD, COPD, CRF, uncomplicated PUD, LC, dyslipidemia, and the use of ASA, NSAIDs, COX-2Is, steroids, clopidogrel, ticlopidine, and warfarin, use of SSRI was an independent risk factor for UGIB (hazard ratio [HR]: 1.97, 95% confidence interval [CI]: 1.67–2.31) and LGIB (HR: 2.96, 95% CI: 2.46–3.57)



- inhibition of serotonin reuptake by platelets leading to depletion of serotonin, which impairs platelet aggregation;17 increased gastric acid secretion and aggravation of NSAID-induced gastric mucosal injury.

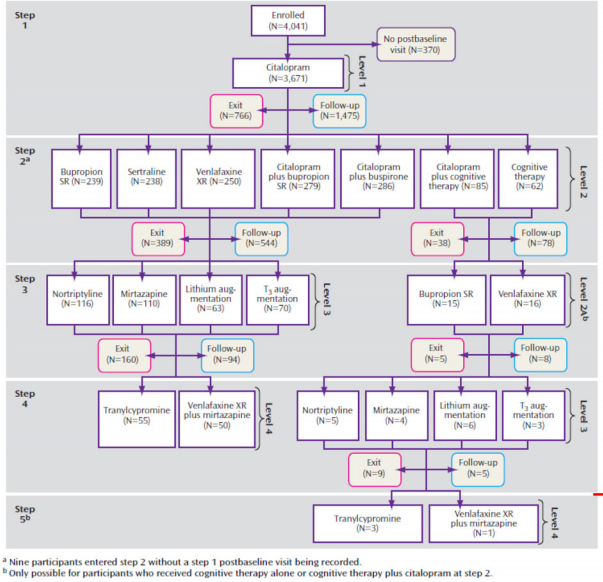
Clin Gastroenterol Hepatol. 2015 Jan;13(1):42-50.e3

Acute Treatment Failure

- Not respond to a medication
  - Side effect
  - An idiosyncratic adverse event
  - Not adequate response
  - Wrong diagnosis
- Acute phase medication trial: 4-6 weeks
  - Partial remission(20-25% reduction) by week 4
  - Lack of partial remission → Treatment change
- Ultimate response check: 8-12 weeks (or longer)
  - Define achievable remission with current ADT
- Response: 50% patients → Needs 2nd medication
  - due to side effect or ineffective response

Synopsis of Psychiatry 11th edition, 2015

FIGURE 1. Overall STAR*D Participant Flow



[a] Nine participants entered step 2 without a step 1 postbaseline visit being recorded.
[b] Only possible for participants who received cognitive therapy alone or cognitive therapy plus citalopram at step 2.

Remission rate

36.8%

30.6%

13.7%

13.0%

총 67%

Serotonin Syndrome in Adults

- CNS: convulsions, disorientation, cognitive impairment
- Neuromuscular: hypertonia, rigidity, myoclonus, hyperreflexia, paresthesia
- Autonomic Instability & Temperature Instability:
- Respiratory distress, tachypnea, hyperthermia, temperature instability, rigors, chills, diaphoresis, tachycardia

Vs NMS : elevations in creatine kinase, liver function tests (LDH, GOT), and WBCs, coupled with a low serum iron level

Serotonin Syndrome. Presentation of 2 cases and review of the literature. Medicine 2000 Jul, 79(4): 201-9
Neuroleptic malignant syndrome versus serotonin syndrome: the search for a diagnostic tool
Ann Pharmacother. 2011 Sep;45(9):e50
Serotonin syndrome vs neuroleptic malignant syndrome: a contrast of causes, diagnoses, and management.
Ann Clin Psychiatry. 2012 May;24(2):155-62.

Discontinuation(withdrawal) syndromes

- Mild sx의 일시적 출현 : paroxetine, venlafaxine, sertraline, fluvoxamine, tricyclic and tetracyclic drug를 포함하는 많은 약물과 연관됨.
- More severe sx : lithium (rebound mania), dopamine-receptor antagonist (tardive dyskinesias), benzodiazepines (anxiety and insomnia)

- **Serotonin discontinuation syndrome**
  - SSRIs 중단과 관계
  - agitation, nausea, dysequilibrium, dysphoria
  - 반감기가 짧을수록, 적어도 2 개월 복용 시, higher dosage 사용 시 더 잘 발생
  - time-limited, 용량을 서서히 감량하면 최소화할 수 있다.

우울증 환자 진료 주의 사항

1. 환자와 첫 만남이 가장 중요함.

환자, 가족, 직장, 친구 관계, 성격, 과거력 등에 대하여 자세히 물어보고 rapport를 잘 형성하는 것이 중요하므로 약 30분간 인터뷰가 필요함.

2. 항우울제의 효과 판정은 척도만으로는 부족하고 **면담을 통하여 평가**.

3. 항우울증에 **가장 소량으로 시작하는 것이** 좋음 (2주 후에 진료한 다음에 증량 여부 결정) Lexapro: 5mg로 시작, Sertraline 25mg로 시작

3. 처음 **3달은 2주에 한번씩 진료해야 함.**

4. 처음 항우울제 치료시 전체 투여 기간은 환자에 따라서 다르지만 **약 1년이 적절.**

5. SSRI 투여 후 행동 문제가 발생할 수 있음(**공격적인 행동, 칼로 찌르려고 하기도함**): 특히 **뇌전증, 파킨슨병에서** 더 자주 발생. 예전에 충동적인 행동을 했던 경우에 더 자주 발생함. →이럴 때에는 SSRI를 중단하고 lamotrigine, valproate 등 기분을 조절하는 약을 사용해야 함.

6. SSRI 투여 후 자살사고가 갑자기 발생할 수도 있으며, 이럴 때에는 **약을 중단.**

7. Stroke, Dementia 환자들에서 SSRI는 **Coagulopathy, SIADH** 등을 유발할 수 있으므로 warfarin을 사용하는 경우에는 특히 조심. Tianeptine (스타브론) 등의 atypical antidepressant를 사용하기도 함.

Courtesy by Prof CHJ

Recommendations for Clinical Specifiers and Dimensions

- Patients under 18 years→Fluoxetine
- Decreased concentration→ vortioxetine
- Cognitive dysfunction→Vortioxetine (Level 1), Bupropion (Level 2), Duloxetine (Level 2), SSRIs (Level 2), Moclobemide (Level 3)
- Decreased sleep quality→ Agomelatine (Level 1), Mirtazapine (Level 2), Quetiapine (Level 2), Trazodone (Level 2), vortioxetine
- Anxiety 동반→desvelafaxine
- Seasonal winter depression: Light therapy
- Menopause with VMS → desvelafaxine
- With somatic symptoms→ Duloxetine (pain) (Level 1), Other SNRIs (pain) (Level 2), Bupropion (fatigue) (Level 1), SSRIs (fatigue) (Level 2), Duloxetine (energy) (Level 2)
- Weight gain→ bupropion
- Sexual dysfunction→ bupropion+ others
- Depression with psychotic feature: ADT + Atypical Antipsychotics
- Caution with pre-existing HTN or underlying conditions by increases in BP × desvelafaxine.
- Caution with risk factors of hyponatremia×desvelafaxine, 65세 이상 +SSRI
- Caution with psychosis×vortioxetine.
- GIB risk, men→ SNRI

Synopsis of Psychiatry 11th edition, 2015
Guidelines for the Pharmacological Management of Depression: Review date Sept 2018, NICE
The Canadian Journal of Psychiatry. 2016, Vol. 61(9) 540-560

CLINICAL BOTTOM LINE: Treatment...

- Depression is highly treatable
- Neurologists play an important role in treatment
- Neurologists familiar with new antidepressants are well-equipped to treat most cases of depression.
- Refer patients to a psychiatrist as needed
- Know options for addressing common side effects