우울증 진단과 치료 Update

나 해 리
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Diagnosis and Treatment of Depression in Late Life: Update

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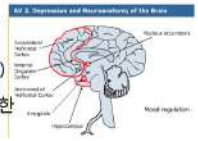
Depression 우울증 (憂鬱症)



- 슬픔은 상실과 슬픈 사건에 대한 반응으로 인간의 정서적 유산의 자연스러운 부분 .cf) 우울증- 병리적 및 기능 장애 상태
- 우울증은 슬프거나, 울적한 느낌이 기분상의 문제를 넘어 신체와 생각의 여러부분까지 영향을 끼쳐 개인이나 사회생활에 영향을 주는 상태
- 증상이 2주 이상 지속될 때
- DSM-IV-TR은 기간과 증상 수에 따라 MDD를 정의.
- 우울증은 이질적인 상태로 간주.
- 뇌의 생물학적 이상은 수면, 식사, 에너지 및 정서적 반응의 문제 발생.

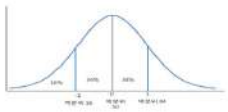
Gelenberg AJ. Depression symptomatology and neurobiology. J Clin Psychiatry. 2010 Jan;71(1):e02.

우울한 기분과 우울증은 다르다

- 우울증은 보다 지속적이다 (2주이상).
- 다른 증상들이 동반된다.
  - 죄책감, 무기력감, 의욕이 없고 거의 모든 활동에서 흥미 저하
  - 체중감소 또는 증가
  - 불면 또는 수면과다 (아침에 일찍 잠에서 깨거나 늦도록 깨어나지 못할때).
  - 정신운동성 초조 또는 지체
  - 피로 또는 에너지 상실
  - 사고 능력 또는 집중력의 저하.
  - 반복적인 죽음에 대한 생각, 자살시도, 계획
- 가족간에 나타나는 경향..자녀에게 대물림 가능성

Depression-정상이란 무엇인가?

- 통계적 기준에 의한 평균 (통계적 정상)
- 한 사회에서 인정되는 정상 (사회적 정상: 이상형)
- 개인적 정상 (예전의 상태와 현재의 상태)
- 관찰자에 의한 상대적 정상 (주관적 판단)



주요우울장애의 DSM-5 진단 기준

■ 1번과 2번 중에 하나는 반드시 포함되고, 다섯 가지 이상이 동일한 2주 동안에 나타난다.

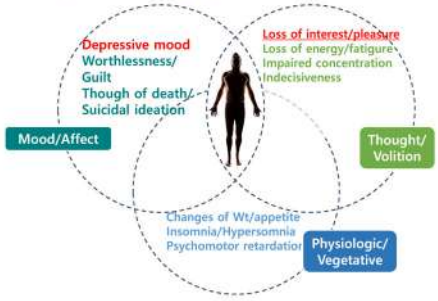
1. 거의 하루종일 우울한 기분이 거의 매일 이어지며, 이는 주관적 느낌 (예컨대 슬픔, 공허감, 아무런 희망이 없음)이나 객관적 관찰 소견(예컨데 자주 눈물을 흘림)으로 확인된다.
2. 거의 하루종일 거의 모든 활동에 대한 흥미나 즐거움 감소된 상태가 거의 매일 이어짐.
3. 체중 또는 식욕의 심한 감소나 증가
4. 거의 매일 반복되는 불면이나 과수면
5. 정신운동의 초조 (예: 안절부절 못함) 또는 지체 (예: 생각이나 행동이 평소보다 느려짐)
6. 거의 매일 반복되는 피로감 또는 활력 상실
7. 무가치감, 또는 지나치거나 부적절한 죄책감이 거의 매일 지속됨.
8. 사고력 또는 집중력의 감퇴, 결정을 못 내리는 우유부단함이 심해져 거의 매일 지속됨.
9. 죽음에 대한 생각이 되풀이되어 떠오르거나, 특정한 계획이 없는 자살 사고가 반복되거나, 자살을 시도하거나, 구체적인 자살 계획을 세움.

■ 임상적으로 의미있는 고통이나 대인관계, 직업을 포함한 주요 영역의 기능 저하를 일으킴.

■ 약물 등 섭취 물질이나 질병으로 인해 야기된 생리적 효과로 인한 것이 아니어야 함.

■ DSM-5의 이전판인 DSM-IV(-TR)에서는 사별에 의한 것이 아니어야 한다고 정의하였으나, DSM-5에서는 삭제됨. 이는 사별 자체가 우울증을 야기하는 매우 중요한 요인이기 때문임. 사별, 경제적 몰락, 자연재해 피해, 중증 질환 등의 심각한 상실 (significant loss)이 있은 이후에 명백한 주요우울증상을 보인다면, 주요우울장애로 진단 내릴 수 있음

Depression Symptoms Clusters



DSM-5 Major Depressive Episode: >5 out of 9, including one of two core X, >2wks, everyday

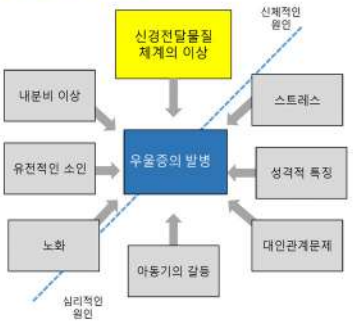
노년기 우울증은 성인 우울증과 임상양상과 의미가 다를 수 있다.

- 주우울증의 증상보다 미약한 증상 (Symptoms beneath 'Major Depression' threshold)
- 슬픔이 없는 우울증 ('Depression without sadness') [1]
- 신체장애와 인지장애로 호소 (Somatic or cognitive focus)
- 정신병적 우울증 (Psychotic depression)
- 혈관성 우울증 (Vascular depression: white matter hyperintensities or leukoencephalopathy, particularly those affecting the frontalstriatal and frontal-limbic brain pathways)
- 뇌졸중 후 우울증 (Post-stroke depression)
- 치매와 우울증 (Depression in dementia)

1. Gallo & Rabins. Am Fam Physician 1999; 60: 820-826

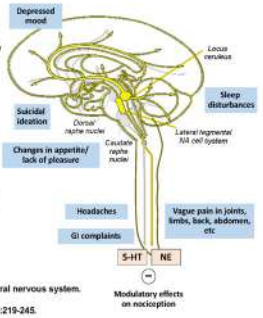
우울증은 왜 생깁니까?

- 가족 중 우울증을 가지고 있을 경우 우울증 발병 위험도가 약 2-3배 상승
- 쌍생아 유전 역학 연구를 통해 우울증의 유전력을 계산했을 때, 유전적인 요인이 약 40% 정도를 기여



5-HT and NE Pathways in the CNS

- 5-HT and NE 경로는 기분, 수면, 인지, 체온조절, 식욕 및 성적 행동을 포함한 뇌의 다양한 기능을 매개[1,2]
- 하강하는 척수 돌출부는 통각을 조절[1,2]
- 이러한 경로의 장애는 우울증의 정서적 신체적 증상과 관련.[2]

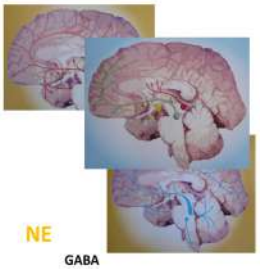


5-HT=serotonin; NE=norepinephrine; CNS=central nervous system.
Adapted from:
1. Fields HL, et al. *Annu Rev Neurosci.* 1991;14:219-245.
2. Stahl SM. *J Clin Psychiatry.* 2002;63:382-383.

ACh

Glu, NMDA

DA 5HT

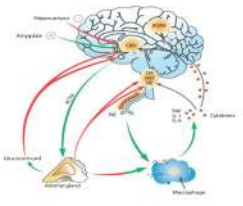


NE

GABA

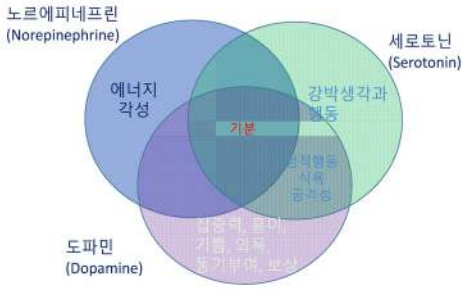
Peptides

Hormones



Chemistry targets

신경전달물질과 정신기능

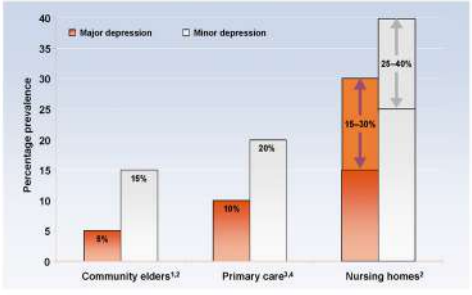


Kaplan HI, Sadock BJ. In: *Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry*. 8th ed. 1998.
Hardman JG, et al. In: Goodman & Gilman's *The Pharmacological Basis of Therapeutics*. 9th ed. 1996.
Nemeroff C. *Scientific American*. June 1998;42-49.

주요우울증의 유병률

- 생애 전주기의 유병률
  - 12-15%
  - MDD with psychotic feature 10-15% of MDD
- Point prevalence according to setting
  - Community-dwelling 1-9%
  - Hospitalized 11-25%
  - Primary Care Settings 10-12%
  - Nursing Home Up to 40%

노년기 우울증의 유병률



1. Gallo & Lebowitz. Psychiatric Services 1999; 50: 1158–1166; 2. Djernes. Acta Psychiatr Scand 2006; 113: 372–387;
3. Friedman et al. Am J Geriatr Psychiatry 2007; 15: 26–41; 4. Zung et al. J Fam Pract 1993; 37 (4): 337–344

국내 우울증 역학
(이미 고혈압 다음으로 2위 > 당뇨병)

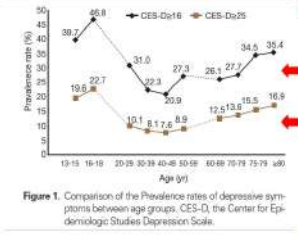


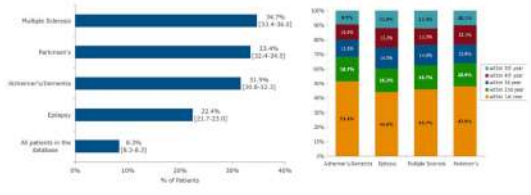
Figure 1. Comparison of the Prevalence rates of depressive symptoms between age groups. CES-D, the Center for Epidemiologic Studies Depression Scale.

- 기존 국내 연구의 수 만명 연구조사의 결과,
  - 우울증이 **유력한 환자** (**25.3-38.9**%)
  - 우울증이 **확실한 환자** (**8.7-21.2**%)
  - 특히 **60세 이상 노인층**에서 **연령에 비례하여 유병율이 증가**

확실한 우울증: 600만명
유력한 우울증: 1,500만명

JH Park, KW Kim, J Korean Med Assoc 2011 April; 54(4): 362-369

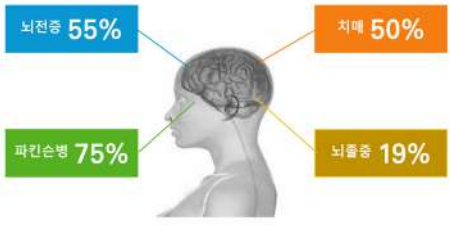
The risk of developing depression when suffering from neurological diseases



Total N=5,381,565
N of Pts with neurological disease=42,914

C. Thefcher et al, GMS German Medical Science 2013, Vol. 11

신경계 주요 4대 질환 별 우울증 유병률



건강보험심사평가원 빅데이터 시스템 2015년 /
Biology Psychiatry 2005;58:175-189 D.L. Evans et al

가장 중요한 두가지 질문

Over the last two weeks:

1. 일을 함에 있어 거의 흥미가 없거나 즐거움이 없다.
   Have you felt little interest or pleasure in doing things?
   (Interest)
2. 기분이 가라앉거나 우울하거나 희망이 없다.
   Have you felt down, depressed, or hopeless? (Mood)

흔히 쓰이는 평가도구들

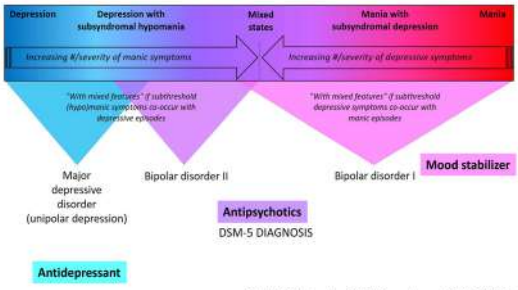
- 자기 보고
  - Geriatric depression scale
  - Beck's depression Inventory
  - Center for Epidemiologic Studies Depression Scale (CES-D)
  - Patient Health Questionaire-2, & -9
- 임상 면담 및 관찰
  - Hamilton Depression Rating Scale
  - Cornell Scale for Depression in Dementia

약물적 치료

- 정확한 진단이 필수
  - 단극성/양극성 우울증인지 감별
- 약물치료의 목표
  - 증상의 관해, 증상의 감소가 아님.
  - 부분 관해시: Relapse ↑, Recurrence ↑, Impairment of daily functioning
- 항우울제의 사용
  - 3-4주 후 임상적 효과
  - 항우울제의 선택: 부작용 고려. 환자의 신체상태, 선호도, 라이프 스타일

Synopsis of Psychiatry 11th edition, 2015

Mood disorders spectrum and DSM–5 diagnosis and 1st line of treatment



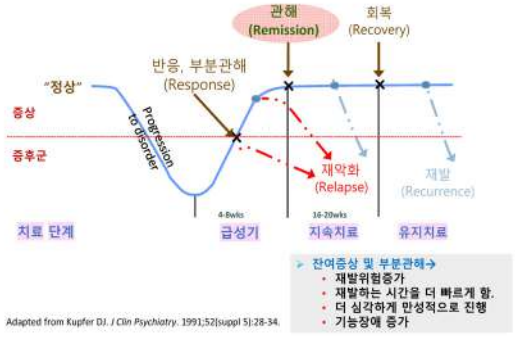
Stahl SM et al. CNS Spectrums (2017), 22.

약물치료의 일반원칙

- 치료실패의 주요 원인
  - 저용량을 충분하지 못한 기간 사용
- 항우울제의 용량
  - 최대 권장용량까지 증량
  - Improvement on a low dosage → Stay → Clinical improvement stop → Raise dosage for a maximal benefit
- 항우울제의 유지기간: at least 4-5 weeks
- 항우울제의 교체
  - 2-3주까지 적절한 반응 없을경우
  - 환자의 실제 복용여부 반드시 확인

Synopsis of Psychiatry 11th edition, 2015

우울증 치료의 목표는 관해(Remission)!



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

급성기 항우울제 치료

Adapted from WPA/PTD Educational Program on Depressive Disorders

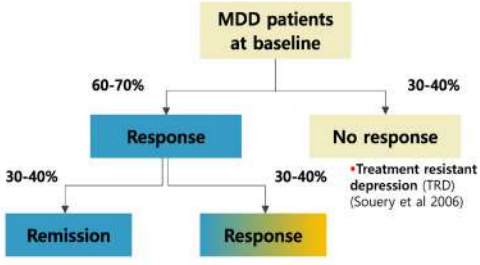
항우울제 처방시 설명

1. 약물 치료가 도움이 될 수 있음을 설명.
2. 증상 호소를 충분히 들어준다
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

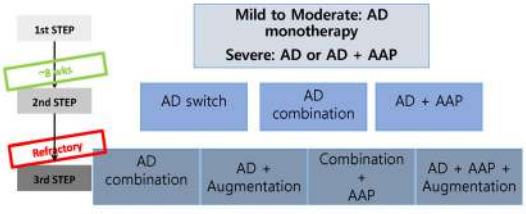
우울증의 급성기 회복과정

1. 수면, 식욕 회복 (수일-2주)
2. 활력호전 (2-3주)
3. 우울 등 주요 증상의 호전 (3-4주 후)
4. 기억력과 판단력의 호전

치료반응: Rule of Thirds



Pharmacotherapy Algorithm for MDD



- AD: antidepressant, AAP: atypical antipsychotics
- Augmentation with
  - Mood stabilizers: Lithium, carbamazepine, valproic acid, lamotrigine
  - CNS stimulants: methylphenidate, dextroamphetamine, modafinil, atomoxetine, etc.
  - Thyroid hormone

Switching Antidepressants

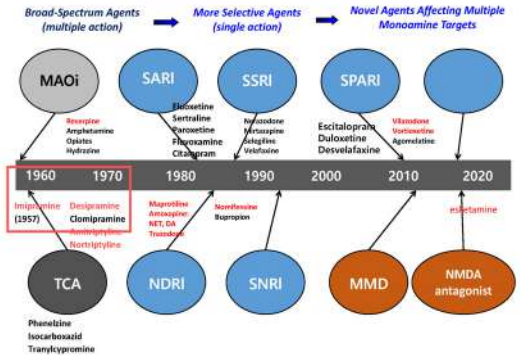
Factors to consider	Potential problems
▪ 스위치 시점 결정 ▪ 1차약제의 현용량 ▪ 약 각각의 효과, transmitter효과, kinetics ▪ 개개인의 부작용에 대한 민감도.	▪ Cholinergic rebound ▪ 항우울제 금단증 ▪ 약물상호작용 ▪ 1차약물의 금단증을 2차약물의 부작용으로 해석할 가능성 ▪ 세로토닌 증후군

치료 기간

- 경증 우울증 (Mild depression):
  - Antidepressants may not be needed as risk-benefit ratio is poor
- 첫번째 삽화 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
- 2번 이상의 삽화 및 일상생활의 기능저하
  - Maintenance treatment at least >2 years
- 어떤 사람은 평생 Some may need lifelong maintenance

Maudsley Guideline11th edition

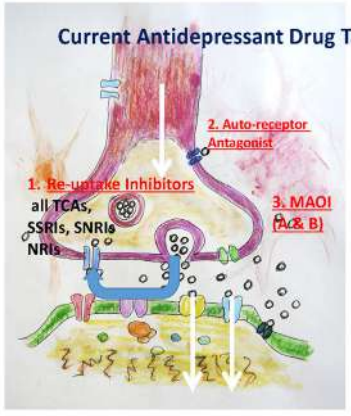
The Evolution of Antidepressants



New Generation Antidepressants

Fluoxetine (Prozac)	**1988**
Bupropion (Wellbutrin IR)	1989
Sertraline (Zoloft)	1992
Paroxetine (Paxil)	1993
Venlafaxine (Effexor), 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), Agomelatine (Valdoxan)	2009
Vortioxetine (Brintellix)	2013

Current Antidepressant Drug Targets



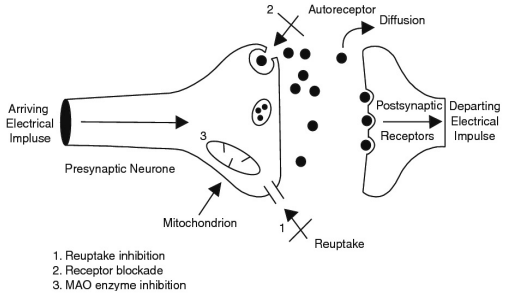
Examples:
1. Amitriptyline, Imipramine
Fluoxetine (Prozac)
Paroxetine (Paxil)
Escitalopram (Lexapro)
Venlafaxine
Duloxetine

2. Mirtarzapine, Mianserin

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

4. Other 5HT receptors

Courtesy by Prof Tang



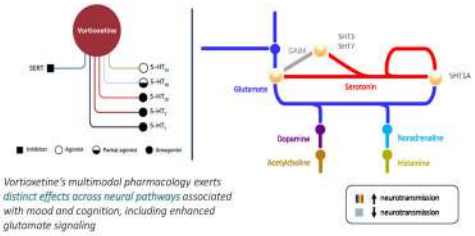
1. Reuptake inhibition
2. Receptor blockade
3. MAO enzyme inhibition

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
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	EsKetamine(스프라바토) Dextromethorphan

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

Vortioxetine (Brintellix®)



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

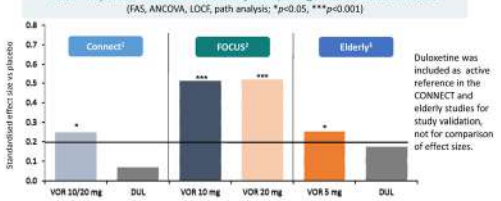
NB. The precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly to humans.

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

Sanchez et al. *Pharmacol Ther.* 2015 Jan;145:43-57;
Feinson et al. *CNS Spectr.* 2014 Apr; 19(2): 133–153

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)

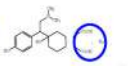


Duloxetine was included as active reference in the CONNECT and elderly studies for study validation, not for comparison of effect sizes.

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.

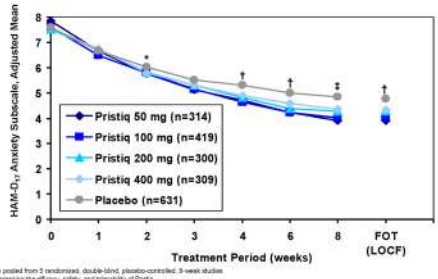
Desvenlafaxine Succinate(Pristiq®)



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≤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 MDD302_HAMDitem, Wyeth Pharmaceuticals.

Agomelatine (Valdoxan®, 아고틴®)

Agomelatine
a new antidepressant with novel phamacology

Stahl SM. Stahl's Essential Psychopharmacology. 3rd ed. 2008 pp. 524A, 541A, 599A; de Bodinat C, et al. Nat Rev Drug Discovery. 2010. , p. 1A , pp. 2A, 4A

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

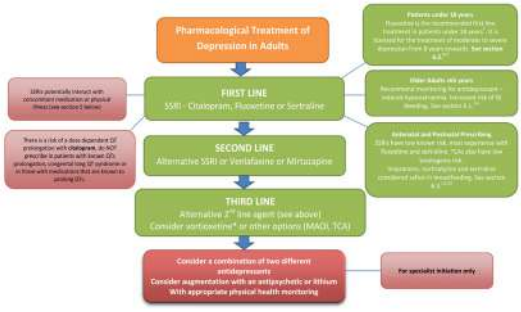
FDA

- 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



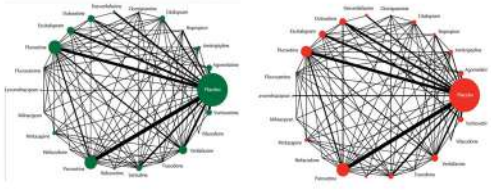
Guidelines for the Pharmacological Management of Depression: Review date Sept 2018, NICE

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 interactions among first-line antidepressants (cytochrome P-450 isoenzyme or p-glycoprotein inhibition noted in brackets)		
Minimal or low potential	Desvenlafaxine Escitalopram/ Citalopram Mirtazapine Venlafaxine	
Moderate potential	Agomelatine (1A2 substrate) Duloxetine (2D6 inhibitor; 1A2 substrate) Sertraline (2D6 inhibitor) Vortioxetine (2D6 substrate)	Bupropion (2D6 inhibitor) Levomilnacipran (3A4 substrate) Vilazodone (3A4 substrate)
Higher potential	Fluoxetine (2D6, 2C19 inhibitor) Moclobemide (MAO inhibitor precautions) Selegiline (MAO inhibitor precautions)	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>

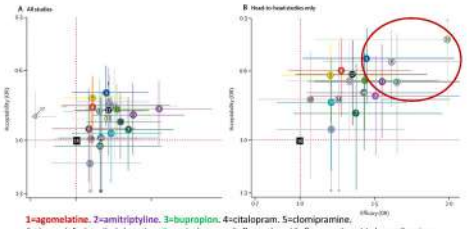


- 522 trials, 116,477 patients and 21 antidepressants were analysed in the acute treatment of adults with major depressive disorder.

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

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.

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[23,24,*] • Tadalafil[23,24,*] • Vardenafil[23,24,*] • Ginkgo biloba[25,26,27,28,29,30] • Bupropion[31,32,33,34] (100 mg × 2)[35]
Category B (No significant effect on sexual functioning)	• Agomelatine[36–38,70] (25 mg)[39] • Desvenlafaxine[39–41] (50 mg)[39] • Moclobemide[42,43,70] (450 mg)[43] • Trazodone[44–46] (150 mg)[39] • Vilazodone[47,48,49,70] (20 mg)[39] • Vortioxetine[41,47,48,49] (20 mg)[50]
Category C (Significant negative effect on sexual functioning)	• Citalopram[51,52] (20 mg)[53] • Clomipramine[51,52] (100 mg)[53] • Escitalopram[52,53,54,55] (10 mg)[56] • Fluoxetine[51,52] (10 mg)[53] • Imipramine[51,52] (50 mg)[53] • Paroxetine[51,52,56] (20 mg)[56] • Phenelzine[51] (15 mg)[53] • Sertraline[51,52] (50 mg)[53] • Venlafaxine[51,52] (75 mg)[53]
Category D (Inconclusive)	• Duloxetine[51,57,70] (60 mg)[52] • Levomilnacipran[54,57] (40 mg)[53] • Mirtazapine[58–71,70] (15 mg)[59]

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

TFK Chokka and FK Hanley. Assessment and management of sexual dysfunction in the context of depression. Ther Adv Psychopharmacol 2015, Vol. 5(1) 13–25

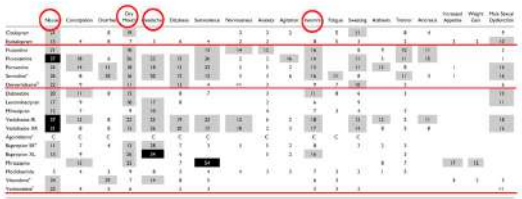
Table 2. Antidepressants and Hepatotoxicity

Agents	Gahr (2015)[10]		Montastruc (2014)[18]							
			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	657 (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)	288 (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 (3.0)	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 (10.0%)	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)

[a]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 25, 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 (%)



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

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	1.5–23.6		1.0–4.9					
Risk group	[Higher risk]		[Moderate risk]			[Insufficient evidence]		

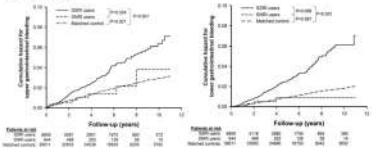
Note: Some case reports involve more than 1 case; all cases are counted separately in this table.
CR = case report; OR = odds ratio.

- 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; increased gastric acid secretion and aggravation of NSAID-induced gastric mucosal injury.

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

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

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.

Adverse drug reactions to ADs

	Adverse drug reactions (ADR) to antidepressants related to their mechanisms of action (1)									Interaction (F&W) (2)
			Precautions and warnings (P&W) highlighted in the full prescribing information by the regulatory agencies(2)							
	Sexual dysfunction (4)	Pathological fractures	Abnormal bleeding	Hyponatremia	Discontinuation syndrome	Mydriasis and increased intraocular pressure (5)	Sustained hypertension (6)	Increased heart rate (5)	Urinary retention (5) (7)	Serotonin syndrome (8)
Serotonergic antidepressants (3)	XXX	X	X	X	XX	—	—	—	—	X
Noradrenergic antidepressants (3)	—	—	—	—	—	X	XX	XX	X	—
Serotonergic and noradrenergic antidepressants (3)	XXX	X	X	X	XX	X	XX	XX	X	X

2. Precautions and warnings (P & W) are in red in this table.
- All ATDs **can ↑ the risk of suicide** in children, adolescents & young adults under 24 yrs old.
- All ATDs can increase the risk of switch towards hypomania or mania.
- Most ATDs **↓ the convulsive threshold. less with mirtazapine & citalopram.**
- **↑ of hepatic enzymes & cases of toxic hepatitis-agomelatine & duloxetine.**

5. With class AIVc drugs this effect is enhanced by the antimuscarinic action.
6. Among drugs with noradrenergic action, →**orthostatic hypotension.**

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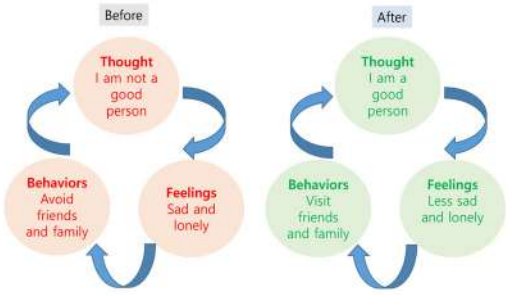
Other Biologic Therapies for Depression

- **ECT (electroconvulsive therapy)**
  - ➢ Refractory geriatric depression, esp. delusional and highly suicidal
  - ➢ Response rate: 70~80%

- **TMS (rTMS):** regional Transcortical Magnetic Stimulation
- **Light Therapy**
  - ➢ Seasonal depression
  - ➢ Insomnia, Changed sleep phase/Delayed sleep onset

Cognitive behavioral therapy (CBT)



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 하기도 함**): 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

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...

- 자세한 병력으로 명확한 진단과 치료 계획
- 신경과 의사는 신경계질환 환자의 우울증 진단과 치료에 전문가이다.
- 약물치료
  - ❑부작용 고려 약제 선택
  - ❑충분한 용량, 충분한 기간(8주 이상), 관해 후 충분한 유지 (6개월-2년)
  - ❑노인은 저용량으로 시작, 천천히 증량.
- 비약물적 치료: 지지적 상담, 교육, 운동, 식이, 수면위생, TMS.
- 중간평가: 진단, 효과, 부작용, 자타해 리스크.
- 필요시 정신건강의학과 전과(정신증을 동반한 우울증, 자살, 비전형적 우울증 등).