Pharmacotherapies for Psychological Trauma

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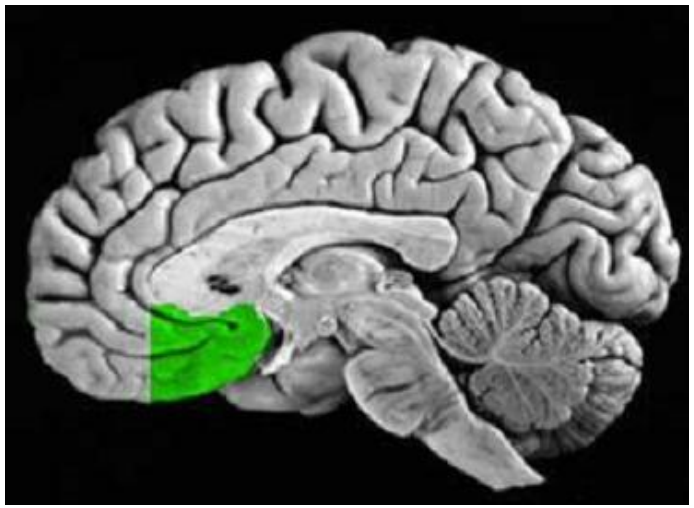
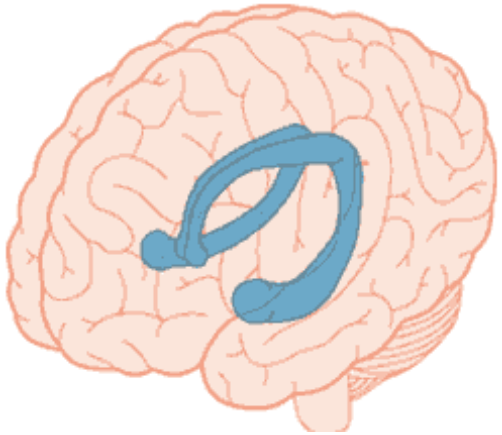
Neurobiology of PTSD

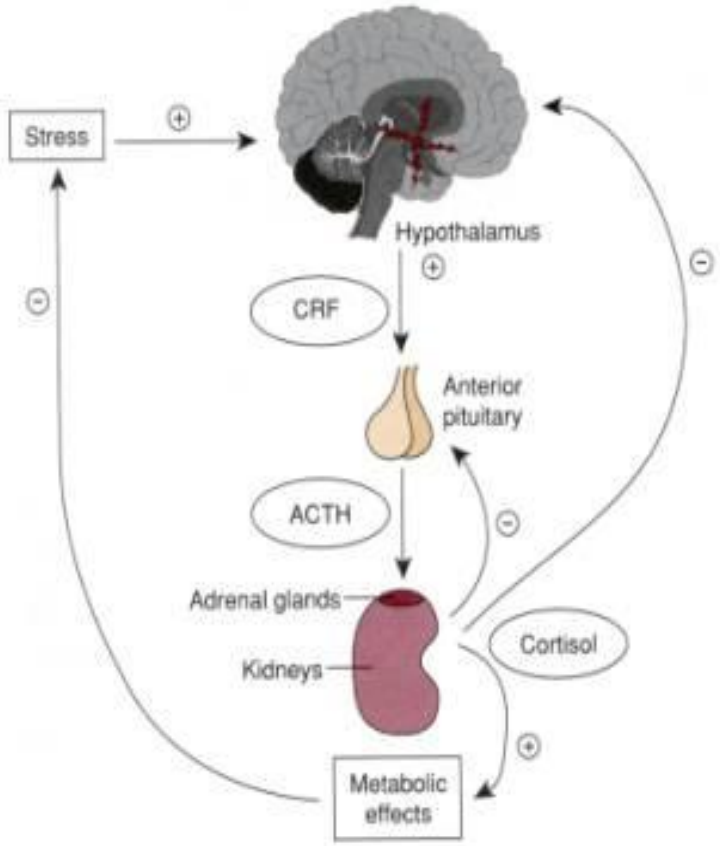
- ? PTSD represents a failure of medial prefrontal/anterior cingulate networks to regulate amygdala activity resulting in hyperreactivity to threat



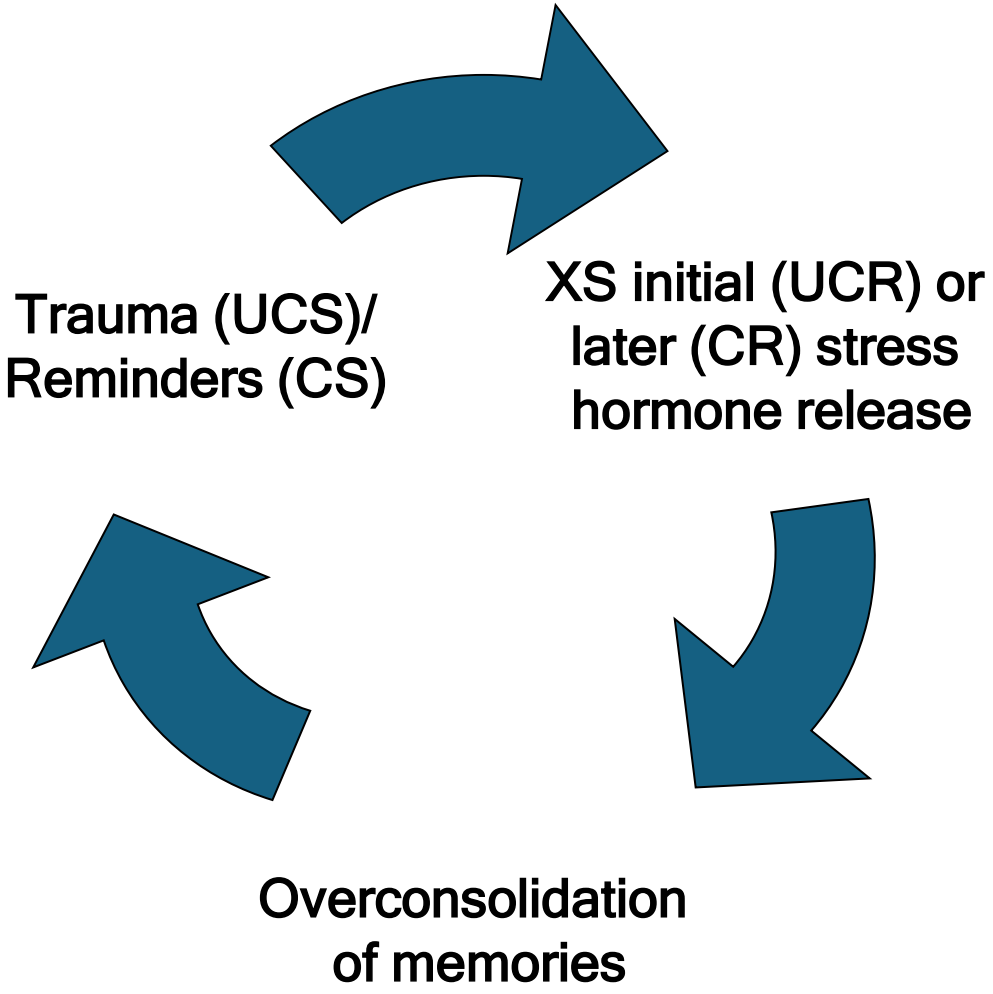


Hypothalamic- Pituitary-Adrenal Axis

- Enhanced negative feedback
- Low cortisol levels
  - Disinhib'n traumatic memory retrieval
  - Failure to contain sympathetic response
- CRF increases locus ceruleus firing and noradrenaline release
- Adrenergic surge consolidates traumatic memories



Positive Feedback Cycle (Pitman, 1989)



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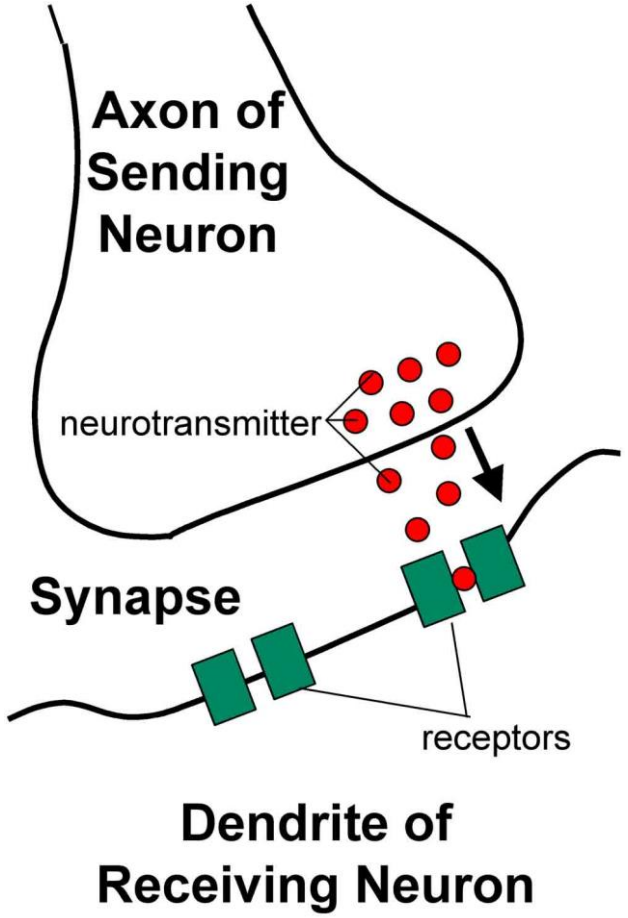
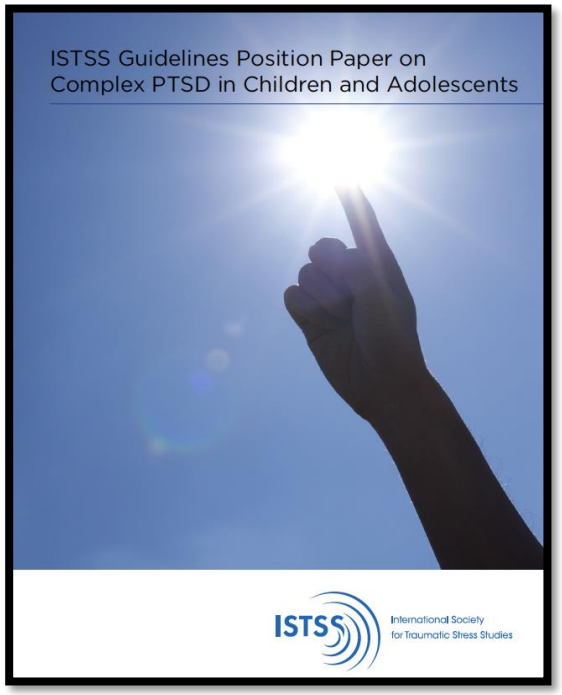
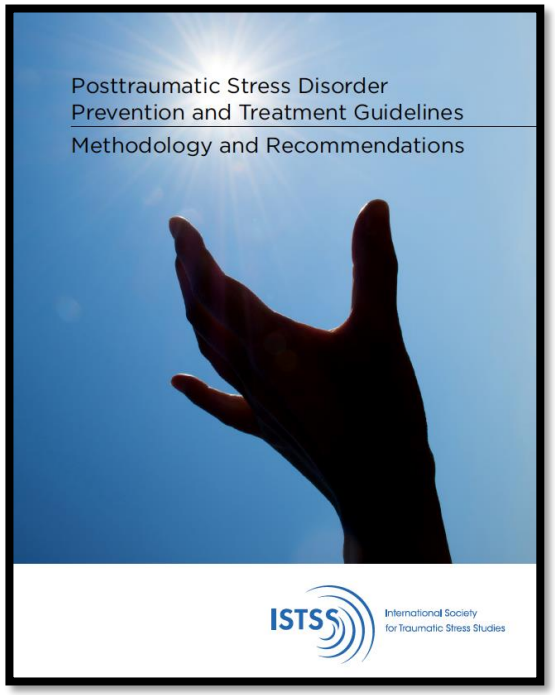
Strategies to Reduce Noradrenergic Overactivity

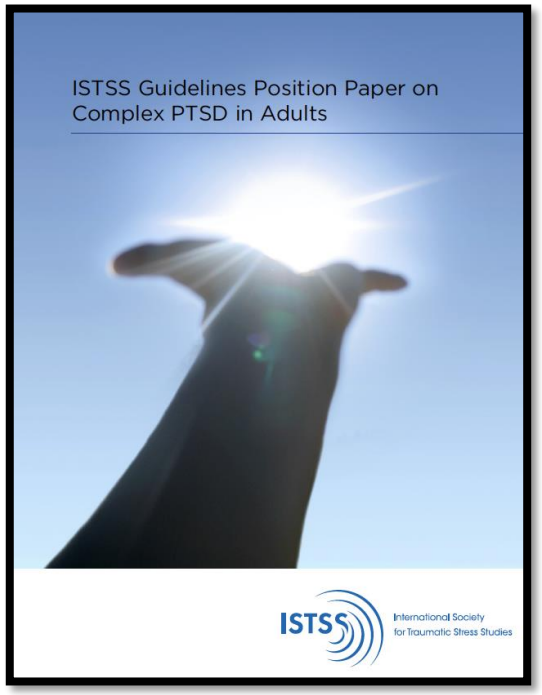
- Direct
  - Alpha 2 adrenergic receptor agonism
    - e.g., clonidine
  - Postsynaptic beta adrenergic blocking
    - e.g., propranolol
  - Alpha 1 adrenergic receptor blocking
    - e.g., prazosin
- Indirect
  - Benzodiazepines, alcohol, gabapentin
  - Cortisol



https://www.istss.org/treating-trauma.aspx







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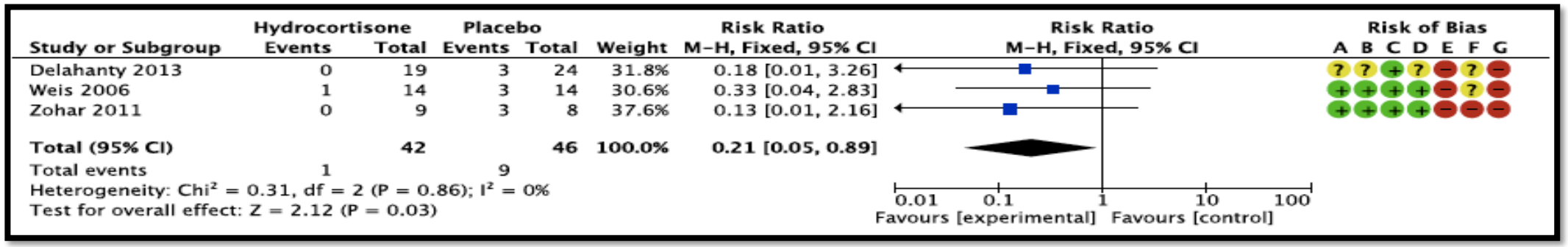
Early Pharmacological Interventions

- Emerging Evidence
  - *Hydrocortisone*
- Insufficient Evidence
  - *Docosahexaenoic Acid*, *Escitalopram*, *Gabapentin*, *Oxytocin*, *Propranolol*



Study or Subgroup	Hydrocortisone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Delahanty 2013	0	19	3	24	31.8%	0.18 [0.01, 3.26]
Weis 2006	1	14	3	14	30.6%	0.33 [0.04, 2.83]
Zohar 2011	0	9	3	8	37.6%	0.13 [0.01, 2.16]
Total (95% CI)		**42**		**46**	**100.0%**	**0.21 [0.05, 0.89]**
Total events	1		9			

Heterogeneity: Chi² = 0.31, df = 2 (P = 0.86); I² = 0%
Test for overall effect: Z = 2.12 (P = 0.03)

ISTSS International Society for Traumatic Stress Studies
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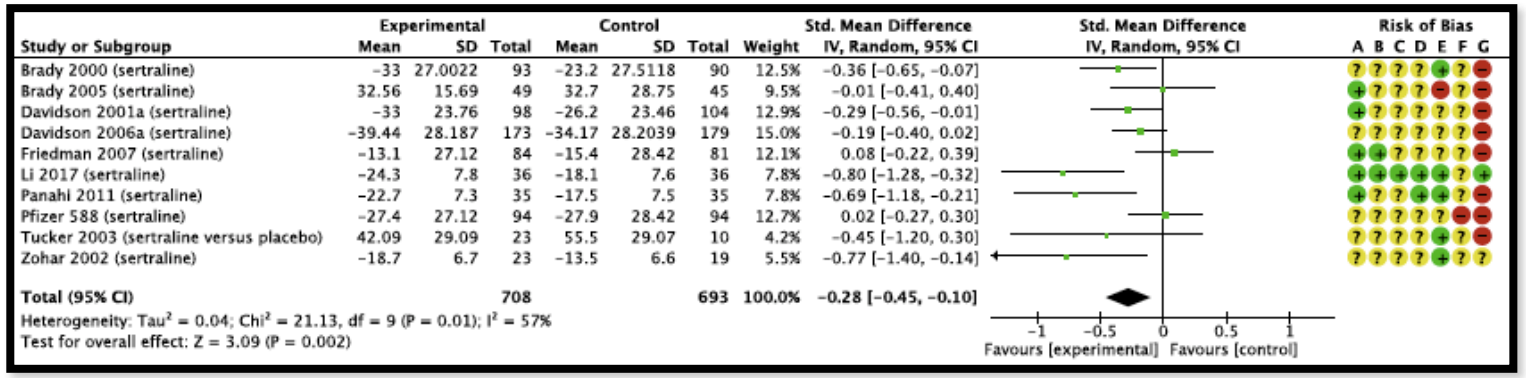
Pharmacological Treatment (Adults)

- Low Effect - *Fluoxetine*, *Paroxetine*, *Sertraline*, *Venlafaxine*
- Emerging Evidence – *Quetiapine*
- Insufficient Evidence to Recommend – *Amitriptyline, Brofaromine, Divalproex, Imipramine, Lamotrigine, Mirtazapine, Olanzapine, Paroxetine, Phenelzine, Tiagabine, Topiramate*



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Brady 2000 (sertraline)	-33	27.0022	93	-23.2	27.5118	90	12.5%	-0.36 [-0.65, -0.07]
Brady 2005 (sertraline)	32.56	15.69	49	32.7	28.75	45	9.5%	-0.01 [-0.41, 0.40]
Davidson 2001a (sertraline)	-33	23.76	98	-26.2	23.46	104	12.9%	-0.29 [-0.56, -0.01]
Davidson 2006a (sertraline)	-39.44	28.187	173	-34.17	28.2039	179	15.0%	-0.19 [-0.40, 0.02]
Friedman 2007 (sertraline)	-13.1	27.12	84	-15.4	28.42	81	12.1%	0.08 [-0.22, 0.39]
Li 2017 (sertraline)	-24.3	7.8	36	-18.1	7.6	36	7.8%	-0.80 [-1.28, -0.32]
Panahi 2011 (sertraline)	-22.7	7.3	35	-17.5	7.5	35	7.8%	-0.69 [-1.18, -0.21]
Pfizer 588 (sertraline)	-27.4	27.12	94	-27.9	28.42	94	12.7%	0.02 [-0.27, 0.30]
Tucker 2003 (sertraline versus placebo)	42.09	29.09	23	55.5	29.07	10	4.2%	-0.45 [-1.20, 0.30]
Zohar 2002 (sertraline)	-18.7	6.7	23	-13.5	6.6	19	5.5%	-0.77 [-1.40, -0.14]
Total (95% CI)			708			693	100.0%	-0.28 [-0.45, -0.10]

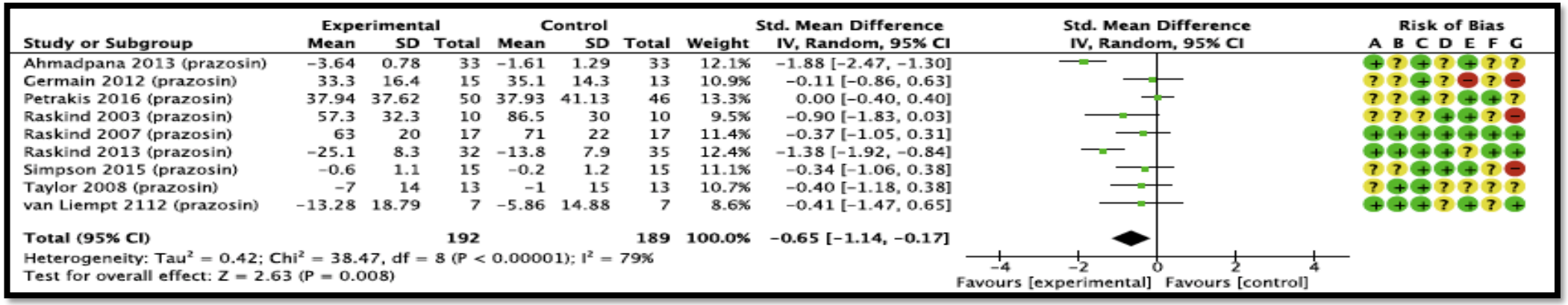
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 21.13$, df = 9 (P = 0.01); $I^2 = 57\%$
Test for overall effect: Z = 3.09 (P = 0.002)

Std. Mean Difference IV, Random, 95% CI: -1, -0.5, 0, 0.5, 1
Favours [experimental] Favours [control]

Risk of Bias: A B C D E F G

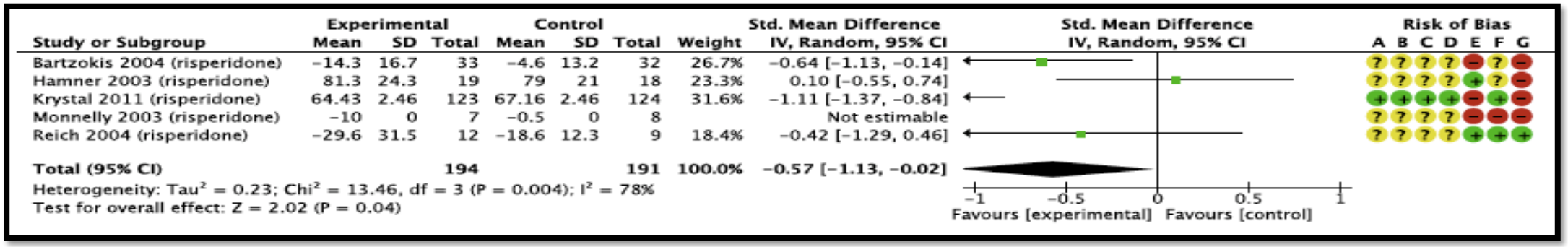
Hoskins MD, et al. (2021) Eur J Psychotraumatol

Pharmacological Augmentation



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ahmadpana 2013 (prazosin)	−3.64	0.78	33	−1.61	1.29	33	12.1%	−1.88 [−2.47, −1.30]
Germain 2012 (prazosin)	33.3	16.4	15	35.1	14.3	13	10.9%	−0.11 [−0.86, 0.63]
Petrakis 2016 (prazosin)	37.94	37.62	50	37.93	41.13	46	13.3%	0.00 [−0.40, 0.40]
Raskind 2003 (prazosin)	57.3	32.3	10	86.5	30	10	9.5%	−0.90 [−1.83, 0.03]
Raskind 2007 (prazosin)	63	20	17	71	22	17	11.4%	−0.37 [−1.05, 0.31]
Raskind 2013 (prazosin)	−25.1	8.3	32	−13.8	7.9	35	12.4%	−1.38 [−1.92, −0.84]
Simpson 2015 (prazosin)	−0.6	1.1	15	−0.2	1.2	15	11.1%	−0.34 [−1.06, 0.38]
Taylor 2008 (prazosin)	−7	14	13	−1	15	13	10.7%	−0.40 [−1.18, 0.38]
van Liempt 2112 (prazosin)	−13.28	18.79	7	−5.86	14.88	7	8.6%	−0.41 [−1.47, 0.65]
Total (95% CI)			**192**			**189**	**100.0%**	**−0.65 [−1.14, −0.17]**

Heterogeneity: Tau² = 0.42; Chi² = 38.47, df = 8 (P < 0.00001); I² = 79%
Test for overall effect: Z = 2.63 (P = 0.008)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bartzokis 2004 (risperidone)	−14.3	16.7	33	−4.6	13.2	32	26.7%	−0.64 [−1.13, −0.14]
Hamner 2003 (risperidone)	81.3	24.3	19	79	21	18	23.3%	0.10 [−0.55, 0.74]
Krystal 2011 (risperidone)	64.43	2.46	123	67.16	2.46	124	31.6%	−1.11 [−1.37, −0.84]
Monnelly 2003 (risperidone)	−10	0	7	−0.5	0	8		Not estimable
Reich 2004 (risperidone)	−29.6	31.5	12	−18.6	12.3	9	18.4%	−0.42 [−1.29, 0.46]
Total (95% CI)			**194**			**191**	**100.0%**	**−0.57 [−1.13, −0.02]**

Heterogeneity: Tau² = 0.23; Chi² = 13.46, df = 3 (P = 0.004); I² = 78%
Test for overall effect: Z = 2.02 (P = 0.04)

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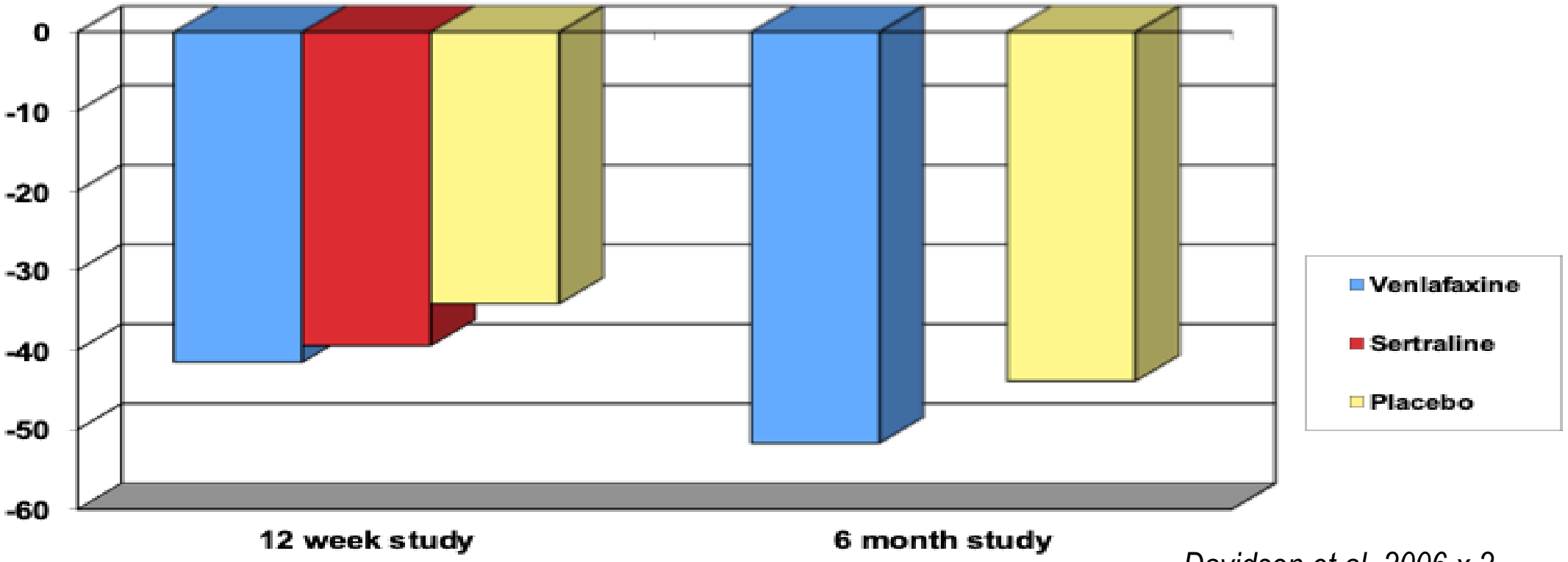
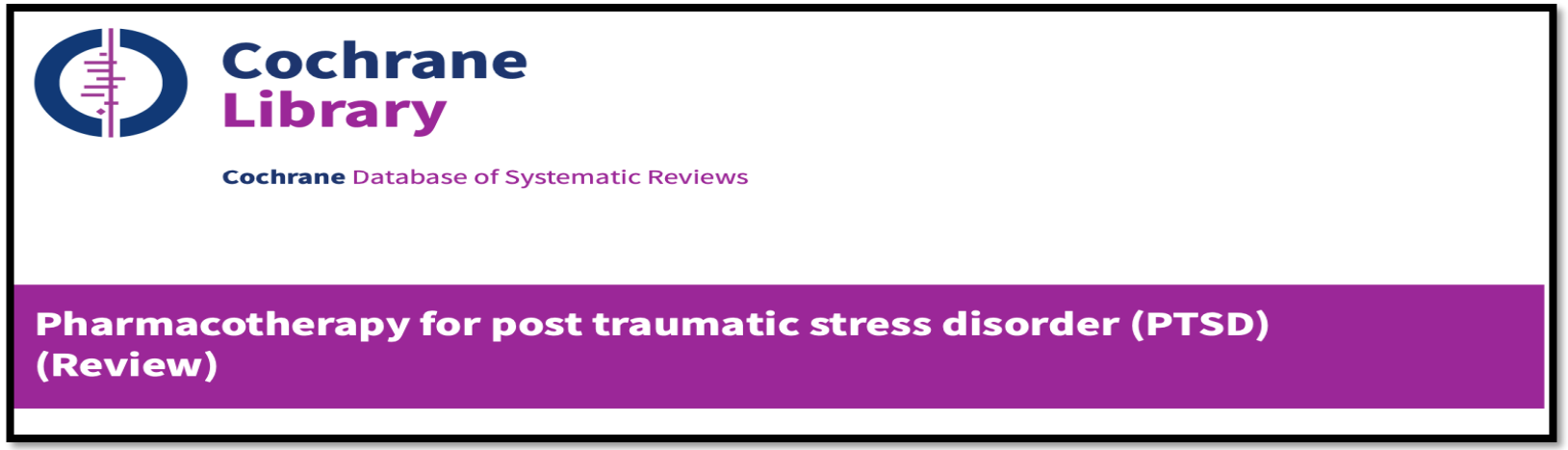
PTSD Symptom Reductions



Davidson et al, 2006 x 2



- Selective serotonin reuptakes inhibitors improve PTSD symptoms
  - moderate-certainty evidence
- Mirtazapine and amitriptyline may improve PTSD symptoms
  - low-certainty evidence
- No evidence for antipsychotic drugs
  - low-certainty evidence
- There remain important gaps in the evidence base

Williams T, et al. (2022)

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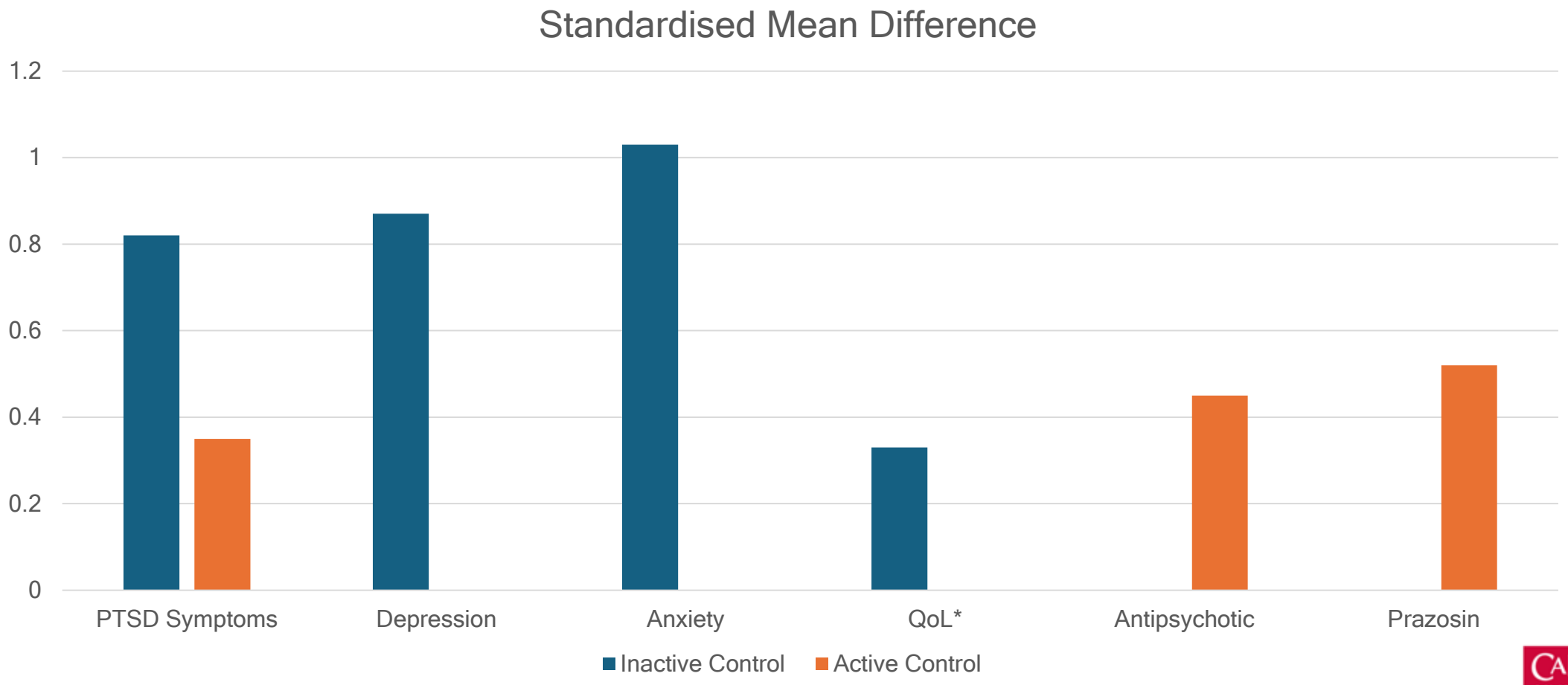
PTSD and Comorbidity after Complex Traumatic Events



Coventry PA, et al. (2021) PLOS Medicine

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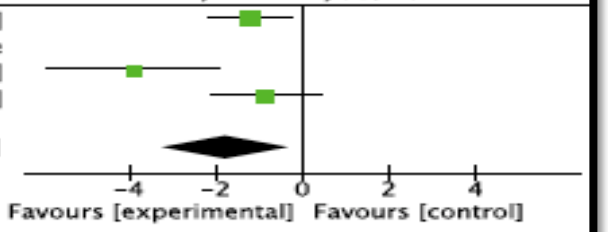
MDMA-Assisted Psychotherapy

- 3,4-methylendioxymethamphetamine
  - Reduces fear of emotional injury
  - Enhances communication
  - Increases empathy

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Mithoefer 2011 (MDMA)	25.5	26.67	12	59.1	26.59	8	39.5%	−1.21 [−2.20, −0.22]
Mithoefer 2018 (MDMA 125mg)	−44.3	28.67	12	−11.4	12.6	7		Not estimable
Mithoefer 2018 (MDMA 75mg)	−58.3	9.78	7	−11.4	12.6	7	25.2%	−3.89 [−5.89, −1.90]
Oehen 2013 (MDMA)	50.8	19.7	8	66.5	7.6	4	35.3%	−0.85 [−2.12, 0.42]
Total (95% CI)			27			19	100.0%	**−1.76 [−3.21, −0.31]**

Heterogeneity: Tau² = 1.14; Chi² = 6.82, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 2.38 (P = 0.02)



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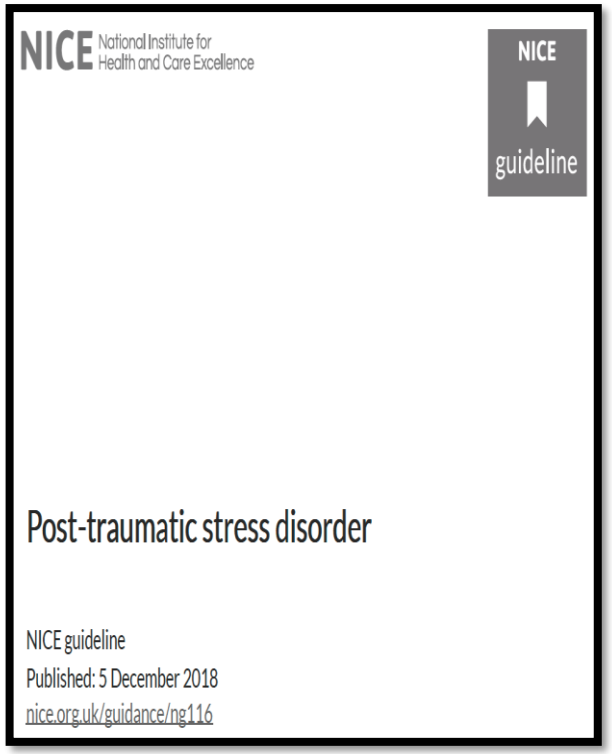
NICE (2018) PTSD Guideline Recommendations

- People under 18
  - Do not offer drug treatments for the prevention or treatment of PTSD
- Adults
  - Do not offer drug treatments to prevent PTSD
  - Consider venlafaxine or a SSRI, such as sertraline, if the person has a preference for drug treatment
  - Consider antipsychotics such as risperidone, in addition to psychological therapies, if:
    - disabling symptoms and behaviours, e.g., severe hyperarousal
    - psychotic symptoms
    - and symptoms have not responded to other drug or psychological treatments.



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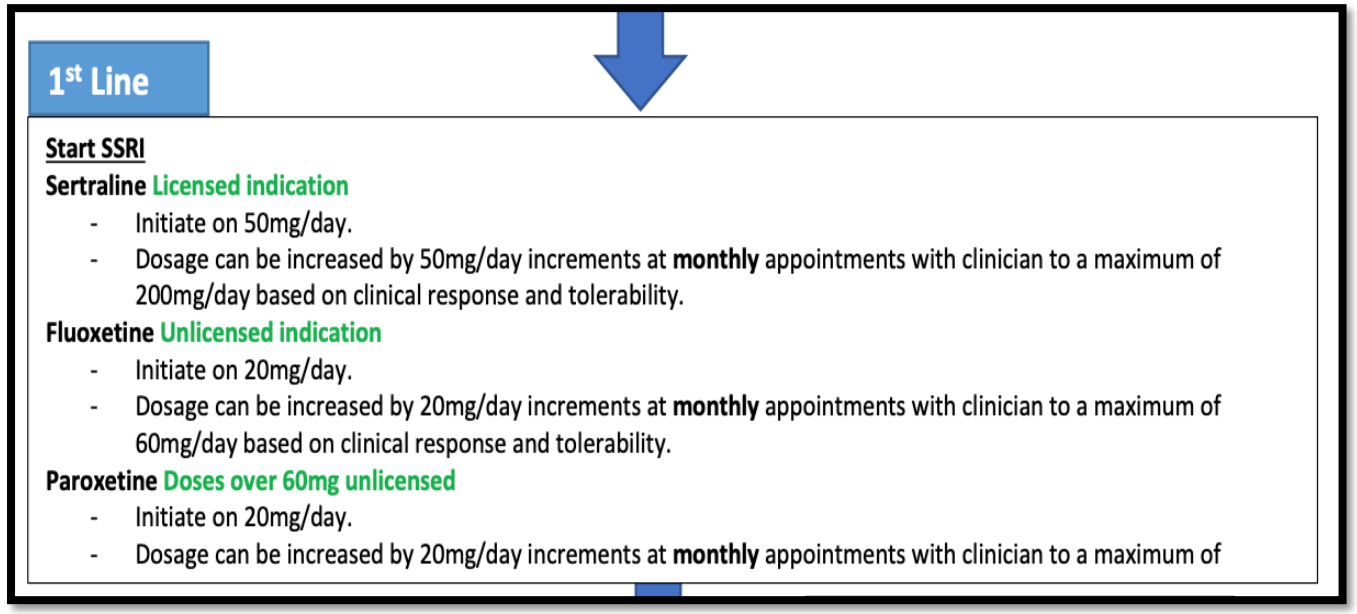
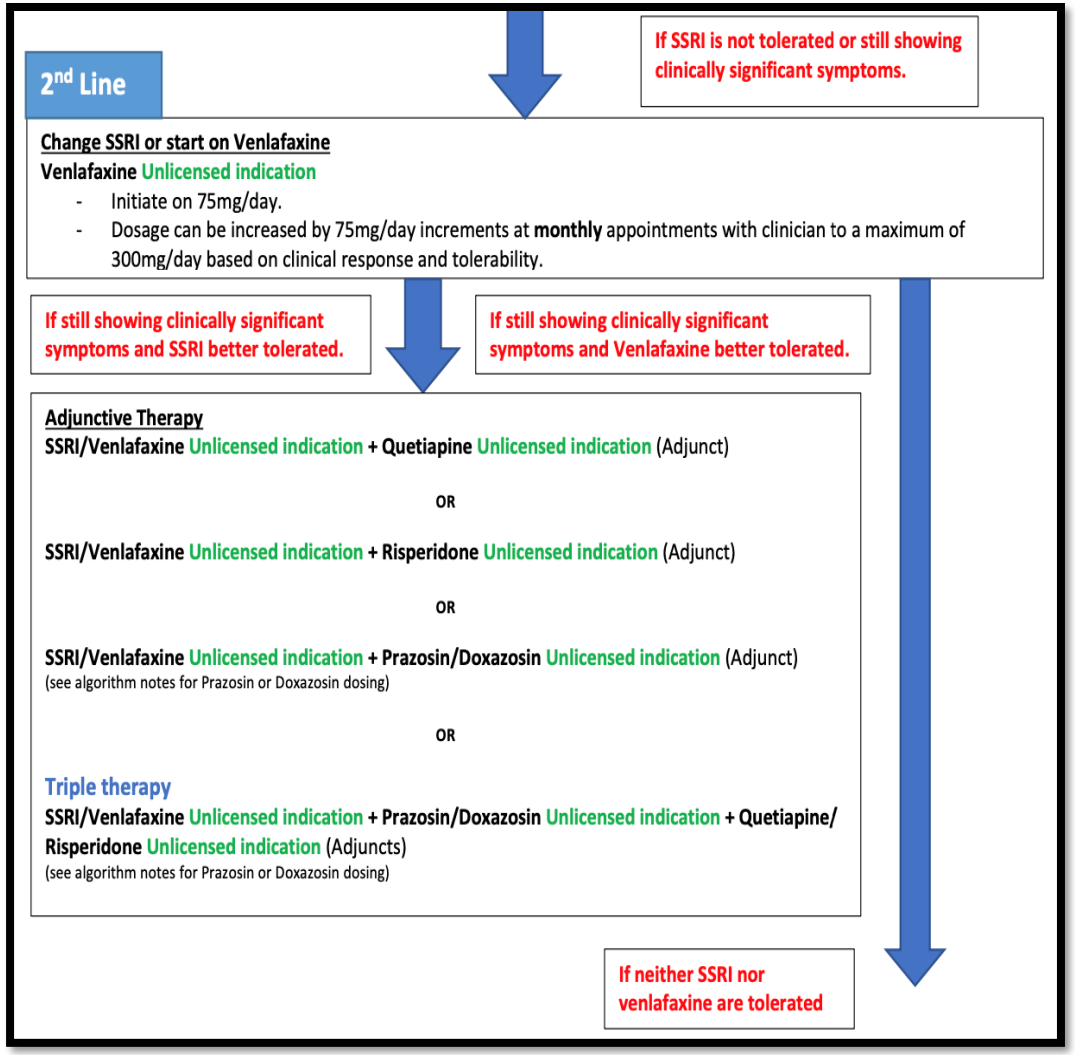
Traumatic Stress Wales PTSD Prescribing Algorithm





Hoskins & Bisson (2024)

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https://traumaticstress.nhs.wales/research-and-improvement/tsw-prescribing-algorithm/

Traumatic Stress Wales PTSD Prescribing Algorithm

Hoskins & Bisson (2024)

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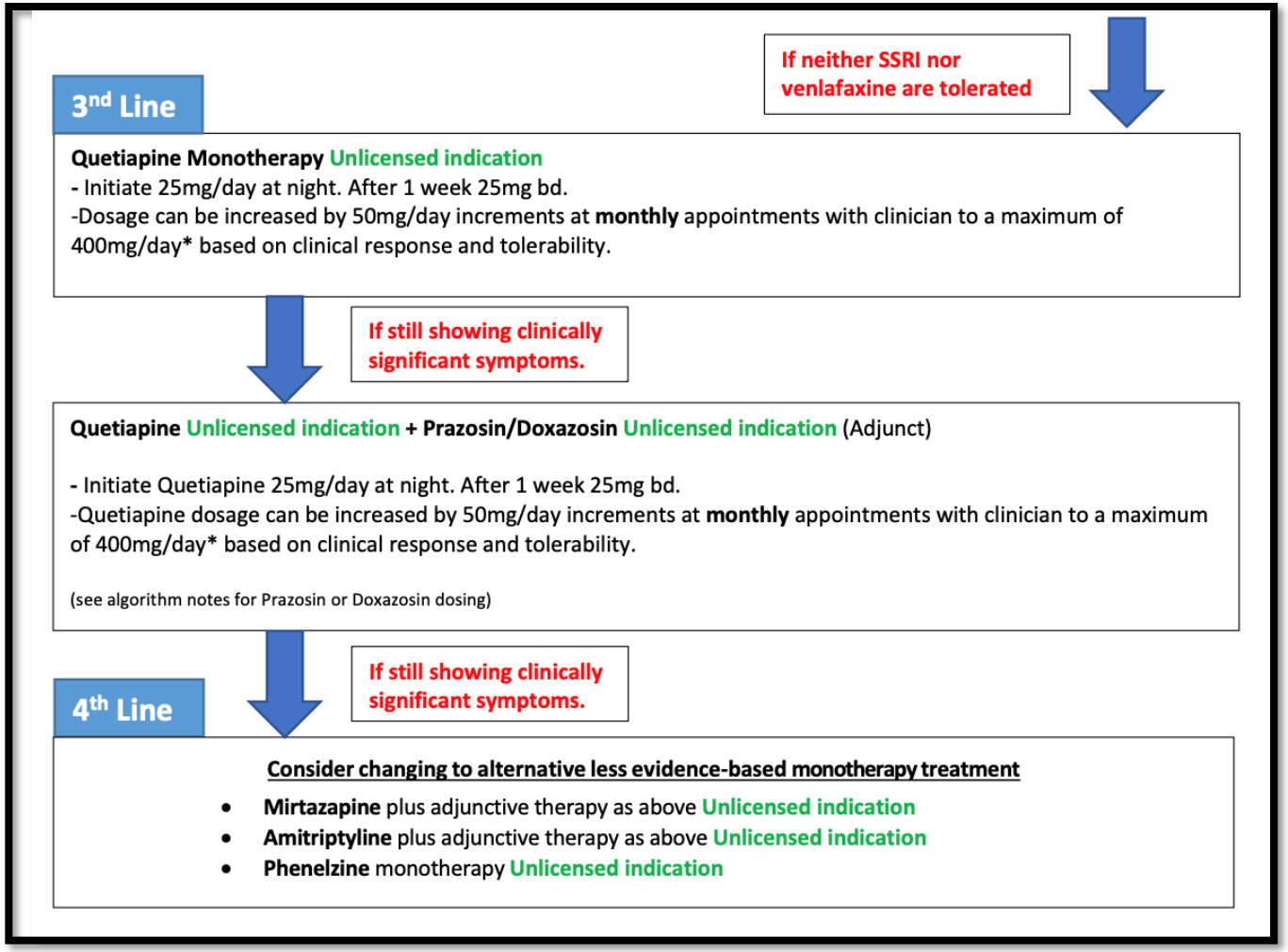

https://traumaticstress.nhs.wales/research-and-improvement/tsw-prescribing-algorithm/

Diolch Yn Fawr

https://www.cardiff.ac.uk/people/view/122802-bisson-jonathan

https://traumaticstress.nhs.wales/

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