Experimentelle Pharmakotherapien in der Psychiatrie

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Experimentelle Pharmakotherapien in der Psychiatrie

• Strategien & Status quo ZNS Drug Development
• Pathogenesemodelle / krankheitsübergreifende neurobiologische Mechanismen
• Neue / Experimentelle Therapieansätze
“CNS Drug Pipelines Are Drying Up”

- If trends continue CNS disorders will make up 14.7% of global disease burden— the largest burden of any disease group
- Only 8.2% of drugs are ultimately approved
- It takes an average of 8.1 yrs and $850 mill in direct costs to get a drug approved
- Companies shy away from safety risks (suicidality, abuse liability, cognitive or motor impairment) and “real-world patients”
- Pathophysiology of most CNS disorders are ill understood

# “The Most Transformative Drugs in the Past 25 Years: A Survey of Physicians”

## Preselection

<table>
<thead>
<tr>
<th>Clinical field</th>
<th>Consensus top selection*</th>
<th>Consensus second-place selection</th>
<th>Notes on results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaesthesiology</td>
<td>Propofol (11)</td>
<td>Remifentanil (2)</td>
<td>Propofol was a clear consensus choice</td>
</tr>
<tr>
<td>Cardiology</td>
<td>Lovastatin (7)</td>
<td>ACE inhibitors (0)</td>
<td>Alteplase (recombinant tPA) came in a close third, receiving fewer second-place mentions than ACE inhibitors</td>
</tr>
<tr>
<td>Dermatology</td>
<td>TNF blockers (7)</td>
<td>OnabotulinumtoxinA (3)</td>
<td>Participants selected multiple TNF blockers, so the drugs were considered as a single class; some participants mentioned the transformative role of isotretinoin, which fell outside our date range for inclusion</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>Bisphosphonates (6)</td>
<td>Metformin (3)</td>
<td>Most participants picked out multiple bisphosphonates, so the individual drugs were collated into a group</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>Omeprazole (6)</td>
<td>TNF blockers</td>
<td>Omeprazole was the runaway choice</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>HIV protease inhibitors (4)</td>
<td>Zidovudine (2)</td>
<td>Participants were inclined to include all of the initial group of HIV protease inhibitors (saquinavir, ritonavir and indinavir)</td>
</tr>
<tr>
<td>Genetics</td>
<td>Algulcerase (4)</td>
<td>Nitisinone (1)</td>
<td>Many participants also chose sodium phenylacetate and sodium benzoate but noted that the use of sodium benzoate pre-dated the time period of this study</td>
</tr>
<tr>
<td>Nephrology</td>
<td>ACE inhibitors (10)</td>
<td>Epoetin alfa (2)</td>
<td>Captopril was selected by the majority of participants, even though it was outside the date range of our study, so the group of ACE inhibitors was collated into one class</td>
</tr>
<tr>
<td>Neurology</td>
<td>Sumatriptan (4)</td>
<td>Interferon beta-1b, interferon beta-1a (4)</td>
<td>Opinion was closely divided between sumatriptan and the interferons</td>
</tr>
<tr>
<td>Oncology</td>
<td>Imatinib (5)</td>
<td>Rituximab (3)</td>
<td>Trastuzumab (3) had fewer second-place mentions than rituximab</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Anti-VEGF agents (7)</td>
<td>Latanoprost (3)</td>
<td>Anti-VEGF agents were collated into a class at the suggestion of several participants</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>Fluoxetine (6)</td>
<td>Clozapine (4)</td>
<td>Opinion was closely divided among these choices, but no other product classes received even a marginal consideration</td>
</tr>
<tr>
<td>Pulmonary medicine</td>
<td>Epoprostenol (1)</td>
<td>Combination Fluticasone and salmeterol (2)</td>
<td>Opinion was closely divided among all choices (including synthetic surfactants, receiving two first-place mentions), with the combination of fluticasone and salmeterol selected for its substantial patient impact rather than its novelty of drug design</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>TNF blockers (11)</td>
<td>Bisphosphonates (1)</td>
<td>Rituximab came in a close third</td>
</tr>
<tr>
<td>Urology</td>
<td>Sildenafil (5)</td>
<td>Tamsulosin (3)</td>
<td>Finasteride (a 5-alpha reductase inhibitor) came in a close third (and received one first-place mention)</td>
</tr>
</tbody>
</table>

ACE: angiotensin-converting enzyme; TNF: tumour necrosis factor; tPA, tissue-type plasminogen activator; VEGF, vascular endothelial growth factor.

*Number of first-place mentions is provided in parentheses.

A.Kesselheim, J Avorn 2013: Nature Reviews Drug Discovery
Development Strategies: Bottom-up

1. “MOA”:
   - Human - / Beobachtungsstudien (Biosamples, Primärzellen)
   - Tierexperimente (Tiermodelle: Biochemie + Verhalten)
   - In-vitro Modelle (Zellkulturmodelle, Zelllinien)

2. Screening, multidimensional:
   - Methodik = HTS (Genom, Transcriptom, Proteom, Funktoinsebenen)

   - Tierexperimente
   - In-vitro (z.B. Zellkulturen, Funktionsassays)
   - Humane Interventionsstudien

4. “Repurposing / Repositioning Strategien”
Development Strategies: Repurposing

• Wichtigster Aspekt beim „Repurposing“?
• Drei Hauptansätze:

  • Entdeckungen in klinischer Praxis („Serendipity“)
    • → Bupropione zur Raucherentwöhnung
  • Kenntnis “vorteilhafter Wirkmechanismen”
    • → Atomoxetine ADHS
  • Kenntnis neurobiologischer Mechanismen psychiatrischer Erkrankungen
    • → anti-entzündliche Interventionen bei Depression
Development Strategies: Repurposing

**DISCOVERY**
- Knowledge-based DR
- Activity-based DR
- *In silico* DR
  - Molecular docking
  - Transcriptional signatures
  - Network analysis
  - Data mining
  - Machine learning
  - Similarity analysis

**VALIDATION**
- *In silico* analysis
  - Retrospective studies
  - Meta-analysis
  - Molecular docking
  - Transcriptional signatures
- *In vitro* analysis
  - Cell culture studies
  - Protein signatures
  - Knock-down gene signatures
- *In vivo* analysis
  - Xenografts

**Clinical trials**
- Phase 1
- Phase 2
- Phase 3
- Phase 4
Fig. 1 Ex vivo CNS drug discovery pipeline.

A Primary PBMCs

B Kinetic profiling

C Drug target identification

D Drug repurposing

E Clinical validation

F Functional stimulation

Fluorescent cell barcoding

Staining phospho-specific cell signaling epitopes

Primary PBMCs

Compound library (up to 80 ligand/vehicle conditions)

Barcoding dyes (up to 80 unique combinations)

Antibody array (up to 79 epitopes)

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Fig. 4 Target identification by functional profiling of cell signaling abnormalities in SCZ T cells.

Santiago G. Lago et al. Sci Adv 2019;5:eaa9093
Fig. 3 Kinetic exploration of neuropsychiatric treatments and novel inhibitors of the Akt/GSK-3β pathway in T cells.

Santiago G. Lago et al. Sci Adv 2019;5:eaau9093

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Fig. 5 Phenotypic drug repurposing based on cellular response.

A. PLC-γ1

B. No interaction • Interaction • Potentiation

C. EC50 (95% CI) [nM]: Compound:

- 151 (98.232) — Nicardipine
- 166 (127.221) — Nitrendipine
- 200 (136.294) — Methyldopa
- 223 (185.266) — Reserpine
- 233 (188.269) — Antipyrine
- 258 (164.465) — Ibutilide
- 270 (219.334) — Chlormepipramine
- 296 (206.397) — Phenergan
- 290 (232.362) — Nimodipine
- 311 (250.380) — Clozapine
- 326 (263.379) — Vehicle

D. Extended FDA library screening

Validation and selectivity testing

Potentiation testing

Santiago G. Lago et al. Sci Adv 2019;5:eaau9093

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Fig. 6 Efficacy of top SCZ drug candidates in human SH-SY5Y neuronal cells.

Santiago G. Lago et al. Sci Adv 2019;5:eaau9093
Anforderung an neue Therapieverfahren

• Im Fokus
  • Therapierefraktäre Verläufe
  • Adhärenz / Compliance (Nebenwirkungen)
  • Ursächliche(re) Therapie („disease modifyer“)

• Ursächliche Therapie
  • Bessere Kenntnis der Pathophysiologie
  • Verbesserte Diagnostik, ggfs.
  • Stratifizierung von Kohorten bis hin zu patientenspezifischen, personalisierten Ansätzen (personalized medicine / precision medicine)
Anforderung an neue Therapieverfahren

- Stratifizierung von Kohorten bis hin zu patientenspezifischen, personalisierten Ansätzen (personalized medicine / precision medicine)

Cartoon modified after: Wills and Lord, Nature Rev Immunology 2015
Anforderung an neue, bessere Therapieverfahren

• Im Fokus
  • Therapierefraktäre Verläufe
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Pathophysiologie - PTSD

- Anderer Stellenwert als Schizophrenie / Affektive Störungen,
- vergleichsweise wenig neurobiologische Grundlagen,
- mehrere aktuelle, experimentelle Ansätze
PTSD – Pathophysiology

Girgenti et al., Biol. Psychiatry 2018
## PTSD – post mortem brain

<table>
<thead>
<tr>
<th>Perturbed Pathway(s)</th>
<th>RNA Source</th>
<th>RNA Analysis</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoid Signaling</td>
<td>PFC (Brodmann area 46)</td>
<td>Candidate transcript qRT-PCR</td>
<td>Zhang et al., 2008 (67)</td>
</tr>
<tr>
<td>SGK1 Signaling</td>
<td>Dorsolateral PFC</td>
<td>Whole-genome microarray</td>
<td>Licznerski et al., 2015 (58)</td>
</tr>
<tr>
<td>Glutamate and Glucocorticoid Signaling</td>
<td>Subgenual PFC (Brodmann area 25)</td>
<td>Candidate transcript qRT-PCR</td>
<td>Holmes et al., 2017 (47)</td>
</tr>
<tr>
<td>Significant eQTL Association With PTSD Risk SNPs</td>
<td>Healthy dorsolateral PFC</td>
<td>RNA-seq</td>
<td>Bharadwaj et al., 2016 (32)</td>
</tr>
</tbody>
</table>

Girgenti et al., Biol. Psychiatry 2018
### PTSD - PBMC

<table>
<thead>
<tr>
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<th>RNA Analysis</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF and Interleukin Signaling</td>
<td>Individuals with PTSD</td>
<td>Customized microarray</td>
<td>Zieker et al., 2007 (37)</td>
</tr>
<tr>
<td><strong>FKBP5</strong>, STAT, and MHC Signaling</td>
<td>Survivors of 9/11</td>
<td>qRT-PCR</td>
<td>Yehuda et al., 2009 (40)</td>
</tr>
<tr>
<td><strong>Monocyte</strong> Gene Signaling</td>
<td>Trauma victims</td>
<td>Customized microarray</td>
<td>Neylan et al., 2011 (39)</td>
</tr>
<tr>
<td>Nuclear Factor and <strong>STAT5B</strong> Signaling</td>
<td>Survivors of 9/11</td>
<td>Microarray</td>
<td>Sarapbas et al., 2011 (41)</td>
</tr>
<tr>
<td><strong>Interleukin</strong> and Stat Pathway Signaling With <strong>FKBP5</strong> SNPs Interacts</td>
<td>Individuals in low-income bracket</td>
<td>Microarray</td>
<td>Mehta et al., 2011 (38)</td>
</tr>
<tr>
<td>Nuclear Factor-kB Signaling Increased</td>
<td>Female child abuse victims with PTSD</td>
<td>qRT-PCR</td>
<td>Pace et al., 2012 (36)</td>
</tr>
</tbody>
</table>
PTSD

Girgenti et al., Biol. Psychiatry 2018
PTSD

Intervention? w/o?
PTSD – Status quo

Review article

Conclusions
Some drugs have a small positive impact on PTSD symptoms and are acceptable. Fluoxetine, paroxetine and venlafaxine may be considered as potential treatments for the disorder. For most drugs there is inadequate evidence regarding efficacy for PTSD, pointing to the need for more research in this area.

A systematic review and meta-analysis of randomised controlled trials was undertaken; 51 studies were included.

Results
Selective serotonin reuptake inhibitors were found to be statistically superior to placebo in reduction of PTSD symptoms, but the effect size was small (standardised mean difference 0.22).

may be considered as potential treatments for the disorder. For most drugs there is inadequate evidence regarding efficacy for PTSD, pointing to the need for more research in this area.

Declaration of interest
None.
PTSD – Neue Therpieansätze
PTSD: D-Cycloserine

- Kommt aus TBC-Therapie (Pilzderivat)
- Wirkt „psychotrop“
- Vermutlich Modulation amygdalärer GLU-Transmission (NMDA partieller Agonist)
- Fördert Extinktionslernen im Tiermodell
- Einsatz in „pharmakoassistierter Psychotherapie“
PTSD: D-Cycloserine

N=12

PTSD: D-Cycloserine

N > 1000: Mataix-Cols et al, JAMA Psychiatry. 2017 May
PTSD: D-Cycloserine

“CONCLUSIONS AND RELEVANCE:
D-cycloserine is associated with a small augmentation effect on exposure-based therapy.”

…
“Further research is needed to identify patient and/or therapy characteristics associated with DCS response.”
PTSD: Prazosin / Doxazosin

- **Alpha1-Antagonist** (Blutdrucksenker)
- Zentral wirksam

---

**Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans**

PTSD: Prazosin / Doxazosin

• **Alpha1-Antagonist** (Blutdrucksenker)
• Zentral wirksam
• “Prazosin... has been effective in **alleviating nightmares** associated with post-traumatic stress disorder (PTSD)”

• **Insgesamt**: Uneinheitliche Studienlage
• Klinisch profitieren einige Patienten sehr gut
• Personalisierte Medizin?
PTSD: MDMA

• 3,4-Methylendioxy-N-methylamphetamin
• Assisted Psychotherapy
PTSD: MDMA

- **3,4-Methylenedioxy-N-methylamphetamine**
- Assisted Psychotherapy
PTSD: MDMA

- 3,4-Methylenedioxy-N-methylamphetamine
- Assisted Psychotherapy
- “further evidence that MDMA-assisted psychotherapy can be used safely and effectively for treating patients with chronic PTSD.”
Pathophysiologie - Schizophrenie

- Schizophrenia
- Affective Disorders (MDD)
- PTSD
Schizophrenie

DA-Hypothese
Four Dopamine Pathways & Schizophrenia

1) Mesolimbic (SCZ – increase in DA causes positive symptoms)
2) Mesocortical (SCZ – DA hypoactivity: negative & cognitive & affective symptoms)
3) Nigrostriatal (Drugs - EPS & TD drug side effects)
4) Tuberohypophyseal (Drugs - hyperprolactinemia side effects)
DA-Hypothesis

→ Symptomatic treatment only
→ Symptom alleviation from targeting
  → mesolimbic pathway (1)
DA-Hypothesis

→ Symptomatic treatment only
→ Symptom alleviation from targeting
  → mesolimbic pathway (1)
→ Side effects from targeting:
  → nigrostriatal pathway (3): EPS
DA-Hypothesis

→ Symptomatic treatment only
→ Symptom alleviation from targeting
   → mesolimbic pathway (1)
→ Side effects from targeting:
   → nigrostriatal pathway (3): EPS
   → tuberoinfundibular pathway (4): Hyperprolactinemia
DA-Hypothesis

- Symptomatic treatment only
- Symptom alleviation from targeting
  - mesolimbic pathway (1)
- Side effects from targeting:
  - nigrostriatal pathway (3): EPS
  - tuberoinfundibular pathway (4): Hyperprolactinemia
  - mesocortical pathway (2): negative symptoms
Schizophrenie

Neuere pathophysiologische Konzepte
• Hohe erbliche Komponente (twin studies, GCTA)
• Polygener Erbgang → "Polygenic / complex disease"

Genes → SCZ → Environment
Genes ↔ Resilienz
• Hohe erbliche Komponente (twin studies, GCTA)
• Polygener Erbgang \( \Rightarrow \) "Polygenic / complex disease"
• Hohe erbliche Komponente (twin studies, GCTA)
• Polygener Erbgang → "Polygenic / complex disease"
• GWAS bei >108 loci → Polygenic Risk Scores ("PRS")
Time Course / Multiple-Hit Theory

Time Course / Multiple-Hit Theory

Placenta

A missing link between genes & environment?
Time Course / Multiple-Hit Theory

Time Course / Multiple-Hit Theory

Neurobiological Processes

Neuronal Differentiation

Neurobiological Processes

Neuronal Differentiation

Synaptic Plasticity

Neurobiological Processes

Neuronal Differentiation

Synaptic Plasticity

"Homeostasis"

Pathophysiologie Schizophrenie - Zusammenfassung

• Veränderte Neurogenese / neuronale Differenzierung
• Veränderte plastizitäts-assoziierte Prozesse
• "Mikrogliale Aktivierung" (Entzündung)
• Verändertes "microenvironment" (gestörte Homöostase)
Schizophrenie – status quo
Schizophrenie – neue Therapieansätze
Schizophrenie

- D3-Rezeptormodulatoren:
  - Aripiprazol, Brexpiprazol, Cariprazine
  - Neuester Vertreter: Cariprazin
  - Längste Halbwertszeit (2-3 Wo.)
  - Möglicherweise gut bei schlechter Compliance

https://stahlonline.cambridge.org/
Schizophrenie

• Cannabinoide?

• increased risk for schizophrenia / psychotic symptoms by high delta-9-tetrahydrocannabinol (THC) / scarcity of cannabidiol (CBD 0–1%)
• CBD (neg. allosteric modulator of CB1-R) ameliorates psychotogenic effects
• CB1 receptor = new pharmacological target?
• CBD: Kein Patentschutz
Schizophrenie

• Anti-entzündliche Ansätze: Minozyklin

Minocycline benefits negative symptoms in early schizophrenia: a randomised double-blind placebo-controlled clinical trial in patients on standard treatment

Imran B Chaudhry¹, Jaime Hallak², Nusrat Husain¹, Fareed Minhas³, John Stirling⁴, Paul Richardson⁵, Serdar Dursun⁵, Graham Dunn¹ and Bill Deakin¹
Schizophrenie: Anti-entzündliche Ansätze

[Graph showing response rates at different weeks for Minocycline and Placebo]
Schizophrenie: Anti-entzündliche Ansätze

• Insbesondere Effekte auf “Negativsymptomatik”

[SANS: Scale for the Assessment of Negative Symptoms]
Schizophrenie: Anti-entzündliche Ansätze

• Weitere Studie Schizophrenie:

Minocycline supplementation for treatment of negative symptoms in early-phase schizophrenia: A double blind, randomized, controlled trial

Fang Liu a,b, Xiaofeng Guo a, Rengrong Wu a, Jianjun Ou a, Yingjun Zheng a, Bingkui Zhang b, Liqin Xie b, Limei Zhang c, Li Yang c, Shuyun Yang c, Junwei Yang c, Ye Ruan c, Yong Zeng b, Xiufeng Xu b, Jingping Zhao a,∗

a Mental Health Institute of The Second Xiangya Hospital, Key Laboratory of Psychiatry and Mental Health of Hunan Province, Central South University, 139 Renmin Middle Road, Changsha, Hunan 410011, China
b First Affiliated Hospital of Hunan Medical University, 295 Xuan Rd., Kunming, Yunnan, China
c Mental Health Center of Yunnan Province, 733 Chuanjin Rd., Kunming, Yunnan, China
Schizophrenie: Anti-entzündliche Ansätze

- Wieder Effekte insbes. auf “Negativsymptomatik”
Minozyklin: Tetrazyklin-Antibiotikum

- anti-entzündlich
- neuroprotektiv
- „pleiotroper“ Wirkmechanismus
- hocheffektiv bei Akne, hemmt MIKROGLIA
Mikroglia

• Proinflammatorische Transformation durch verschiedene Stimuli (Trauma, Infektion...)
• Enge Interaktion mit Neuronen / Astroglia Kettenmann, Neuron, 2015
• Beteiligt an neuronaler Plastizität Kettenmann, Neuron, 2015
• Mediator neuroprotektiver Prozesse (ApoE-Synthese) Clemens et al, J Alz Dis 2017
• Veränderte metabolische Prozesse bei M1 Transformation...
Pathophysiologie - Depression

Schizophrenia

Affective Disorders (MDD)

PTSD
MDD / Affective Disorders

Duman, ... Krystall, Nature Medicine 2016
MDD / Affective Disorders

• Monoamine Hypothesis
MDD / Affective Disorders

• Monoamine Hypothesis
• HPA-Axis
Cortex (cognitive modulation)

Cingulate gyrus (threat perception)

Increased CRH

Amygdala (threat perception)

Hypothalamus

Increase in cerebrospinal fluid

Size decreased
Brain-derived neurotrophic factor reduced
Neurogenesis reduced

Anterior pituitary

Corticotropin (through blood)

Size increased

Adrenal cortex

Cortisol

Size increased

Increased under some conditions

Feedback inhibition

MDD / Affective Disorders

- Monoamine Hypothesis
- HPA-Axis
- Neurogenesis
MDD / Affective Disorders

- Monoamine Hypothesis
- HPA-Axis
- Neurogenesis

Table 1 Overview of studies correlating neurogenesis in the DG and neuropsychiatric disorders. Given that more than 2,000 publications have contributed to the correlative findings summarized here, review publications are primarily cited in Table 1 to direct the reader to comprehensive and referenced tables in the literature.

<table>
<thead>
<tr>
<th>Correlated with neuropsychiatric disorders</th>
<th>Stage of neurogenesis (human postmortem)</th>
<th>Hippocampal</th>
<th>Normalize/improve with treatment? (human/rodents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depressive disorder</td>
<td>Decreased/nc\textsuperscript{133-135}</td>
<td>Decreased\textsuperscript{*104}</td>
<td>Decreased\textsuperscript{136}</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Increased\textsuperscript{125}</td>
<td>Decreased (trend)\textsuperscript{125}</td>
<td>Decreased/nc\textsuperscript{137,138}</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Decreased\textsuperscript{132,135}</td>
<td>Decreased\textsuperscript{142}</td>
<td>Decreased\textsuperscript{143}</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>–</td>
<td>–</td>
<td>Decreased\textsuperscript{145}</td>
</tr>
<tr>
<td>Substance-related and addictive disorder</td>
<td>Decreased\textsuperscript{146}</td>
<td>Decreased#146</td>
<td>Decreased/nc\textsuperscript{147,148}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased\textsuperscript{A95}</td>
<td></td>
</tr>
</tbody>
</table>

Asterisk (*), fewer DG granule neurons in MDD versus MDD with medication and controls; \#decreased dendritic arborization of immature neurons in heroin addicts; carat (\^), increased connectivity between hippocampus and reward-related brain regions. nc, not changed; dash (-), not studied.

Yun et al., ...Eisch, Nat. medicine 2016
MDD / Affective Disorders

- Monoamine Hypothesis
- HPA-Axis
- Neurogenesis

Yun et al., ...Eisch, Nat. medicine 2016
MDD / Affective Disorders

- Monoamine Hypothesis
- HPA-Axis
- Neurogenesis
- Neurotrophins
MDD / Affective Disorders

- Monoamine Hypothesis
- HPA-Axis
- Neurogenesis
- Neurotrophins

Krishnan, Nestler, Nature 2008
MDD / Affective Disorders

- Monoamine Hypothesis
- HPA-Axis
- Neurogenesis
- Neurotrophins
- Synaptic Plasticity
MDD / Affective Disorders

- Monoamine Hypothesis
- HPA-Axis
- Neurogenesis
- Neurotrophins
- Synaptic Plasticity
MDD / Affective Disorders

- Monoamine Hypothesis
- HPA-Axis
- Neurogenesis
- Neurotrophins
- Synaptic Plasticity
- Inflammation
Altered Tryptophane Metabolism:
- Increased QA synthesis = excitotoxicity
- Decreased 5-HT synthesis

Proinflammatory phenotype:
Characteristic cytokine secretion

“Activating Stress”
- HPA dysregulation
- Altered microenvironment
- Sustained pro-inflammatory stimuli
- Decreased endogenous anti-inflammatory mediators

Miller, Nat Rev Immunol, 2016
Altered Tryptophane Metabolism:
• Increased QA synthesis = excitotoxicity
• Decreased 5-HT synthesis

Altered Retinoic Acid Metabolism:
• Increased RA degradation = loss of neuroprotection, pro-inflammatory

Proinflammatory phenotype:
Characteristic cytokine secretion

“Activating Stress”
• HPA dysregulation
• Altered microenvironment
• Sustained pro-inflammatory stimuli
• Decreased endogenous anti-inflammatory mediators

Vicious Cycle:
Sustained pro-inflammatory, depression-associated microenvironment

Hellmann-Regen, ..., Heuser et al., JNI 2015
MDD / Affective Disorders

- Monoamine Hypothesis
- HPA-Axis
- Neurogenesis
- Neurotrophins
- Synaptic Plasticity
- Inflammation /
- Microglial transformation

PET Study

Setiawan et al., JAMA Psychiatry, 2015
MDD / Affective Disorders

• Monoamine Hypothesis
• HPA-Axis
• Neurogenesis
• Neurotrophins
• Synaptic Plasticity
• Inflammation /
• Microglial transformation

Kettenmann et al. Neuron 2013
MDD / Affective Disorders

- Monoamine Hypothesis
- HPA-Axis
- Neurogenesis
- Neurotrophins
- Synaptic Plasticity
- Inflammation /
- Microglial transformation

Andrew Miller, Charles Raison Nat Rev Immunol, 2016
GWAS MDD: Synapse und Immunsystem
Depression – status quo
Depression – Neue Therapieansätze
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• 1) Schnellerer Wirkeintritt („RAAD“)
• 2) Wirksamkeit bei Therapieresistenz
• 3) Weitere Ansätze
  • „Konventionell“, mit weniger UAW
  • Neurosteroide
  • Halluzinogene
Rapid-acting anti-depressants: Ketamin
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**Ketamine**
- 0.5 mg/kg *intravenous* (i.v.) *ketamine* infused over 40 min
- RAAD effects of a single ketamine infusion in MDD (*McGirr et al., 2015*).
- Concerns regarding the efficacy of the treatment blinding
- Repeated administration (e.g., twice per week) appears to maintain the RAAD effects (*Singh et al., 2016*).
- adverse events are transient (1–2h) and typically well tolerated.
- Limitation is addiction liability and the scarcity of data regarding the safety of chronic treatment
- The latter is particularly important considering the association of heavy daily use of ketamine with ulcerative cystitis, *hepatotoxicity*, and *neurotoxicity*
- pilot evidence suggested that *intranasal*(i.n.) administration of ketamine may exert RAAD effects (*Daly et al., 2018*),
- FDA approval for intranasal S-Ketamine in June 2019
S-Ketamine intranasal

- S-Enantiomer des „normalen“ (racemic) Ketamins
- „Better tolerated“ (?) in der Anästhesie sowie im antidepressiven Setting („...less psychotomimetic effects“)
- Allerdings: R-Enantiomer habe ebenfalls antidepressive Effekte bei WENIGER psychotomimetischen Effekten im Tierversuch gezeigt.
- Frage: Wie verhalten sich R- vs. S-Ketamin human?
From: Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study

*p=0.020.
From: Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study
Rapid-acting anti-depressants: Weitere Targets
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(1) Scopolamine (3 i.v. infusions separated by 3–4 days) has shown efficacy compared to placebo in small clinical trials (Drevets, Zarate, & Furey, 2013);

(2) Traxoprodil showed efficacy at day 5 following single infusion in a proof of concept study (Preskorn et al., 2008), yet its development was stopped due to incidence of QT prolongation (Machado-Vieira, Henter, & Zarate, 2017);

(3) Esketamine, the S enantiomer of ketamine, appears to have RAAD properties following i.v. or i.n. administration in early studies (Canuso et al., 2018; Daly et al., 2018; Singh et al., 2016);

(4) Low doses of d-cycloserine, with NMDAR partial agonist effects, were reported to exert RAAD effects in retrospective investigations (Kim, Kushner, Yoon, Anker, & Grant, 2016);

(5) Rapastinel (i.v.) has shown efficacy in a proof of concept study (Preskorn et al., 2015);

(6) Lanicemine, a low-trapping NMDAR antagonist, has shown efficacy in one phase II study but failed in a second larger clinical trial that may have been complicated by high placebo response rates (Sanacora et al., 2013, Sanacora et al., 2017; Zarate et al., 2013).
Therapieresistenz

Depression

Entzündung

↑↑↑

TRD
Minozyklin, Retinsäure und Mikroglia

- anti-entzündlich
- neuroprotektiv
- pleiotroper Wirkmechanismus unbekannt
- hocheffektiv bei Akne
MINO-TRD: From Bedside to Bench – and Back

- Intervention targeting “inflammatory depression”
- Homogeneous sample
- Multicenter-RCT
- 6 weeks, 200 mg/day

Who responds?
- Inflammatory status pre- and post treatment?
- Pre-treatment resting-state fMRI

Treatment of patients: clinical assessment, imaging, genetics, in-vivo
- Use and validation of predictive biomarkers
- Neurobiology-derived entities (patterns)
- Target Engagement: TX development → Precision Psychiatry

Treatment of cells: biochemical assessment, ex-vivo
- Anti-inflammatory actions of minocycline ex vivo
- Transcriptomics, proteomics, metabolomics → Identification of minocycline’s mechanism of action
Weitere Ansätze: „Weniger Nebenwirkungen“
Weitere Ansätze: Neurosteroider

Progesterone → 5α-DHP → Allopregnanolone (SAGE-547 = Neurosteroid)
Allopregnanolone / SAGE-217

Sage Therapeutics Announces Brexanolone Achieves Primary Endpoints in Both Phase 3 Clinical Trials in Postpartum Depression

- Statistically significant mean reduction in the HAM-D score compared to placebo at 60 hours demonstrated in both trials.
- Brexanolone provided a rapid and durable reduction over 30 days in depressive symptoms as measured by HAM-D in both placebo-controlled multi-center trials.

Sage Therapeutics Reports Positive Top-line Results from Phase 2 Placebo-Controlled Trial of SAGE-217 in Major Depressive Disorder

- SAGE-217 met primary endpoint and provided rapid, profound and durable effects through 2-week treatment period and additional 4-week follow-up.
- Well-tolerated and demonstrated highly statistically significant mean reduction in the HAM-D score compared to placebo at 15 days (p<0.0001) beginning after one dose and
Halluzinogene
Halluzinogene

• 26 severe, unipolar, TRD ➔ two oral doses of psilocybin (10 and 25 mg, 7 days apart)
• Depressive symptoms assessed to 6 months post-treatment

Mean QUIDS / Cohen’s $d$
Diskussion