What to Try When You Are Out of Ideas

Repositioning: The Stanley Experience

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DIFFERENT APPROACHES

- Over the past 20 years the Stanley Medical Research Institute (SMRI) has funded approximately 400 clinical trials.
- As SMRI is not a drug company, but rather a charitable organization, we do not develop drugs from scratch, rather use compounds already existing. Hence, de facto all of our clinical trials are repurposing projects.

INFLAMMATORY ETIOLOGY

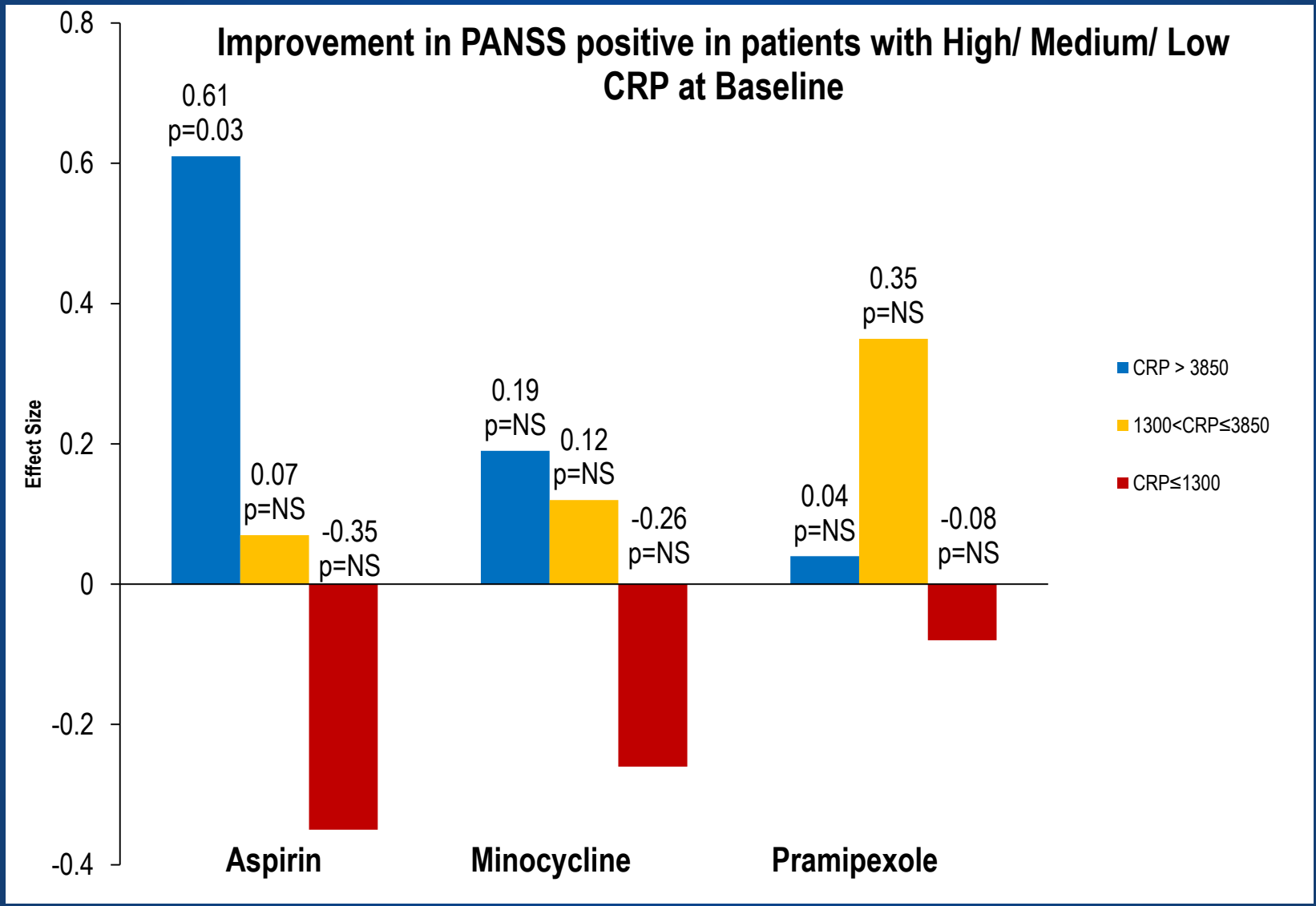
Main focus on drugs which effect the inflammatory response using different mechanisms.

<u>Anti-inflammatory agents tested:</u>

NSAIDs:

- Celecoxib
- Naproxan
- Aspirin
  - Currently being tested in patients with schizophrenia who present high levels of inflammation, as can be seen by high levels of plasma CRP

CRP LEVELS AND OUTCOME



OTHER ANTI-INFAMMATORY AGENTS TESTED

- Prednisone
  - Currently being tested.
- Methotrexate
  - Study is finished, currently analyzing results.
- IV IgG: about to get started
- Mesenchymal Stem Cells-recently funded
  - Stem cells which modulate immuno-regulatory properties by expressing immunosuppressive molecules and various growth factors

ANTIBIOTICS/ANTIVIRALS/ANTIMALARIAL/ ANTITOXOPLASMA

- Minocycline
- Doxycycline
- Valacyclovir
- Azithromycin
- Artemisinin
- Trimethoprim-sulfamethoxazole

MONOCLONAL ANTIBODIES

Monoclonal antibodies currently tested:

- Rituximab (Mab-thera) target: protein CD20 (present on b cells)
- Infliximab (Remicade) target: TNF-α
- Canakinumab (Ilaris) target: IL-1 β
- Tocilizumab (Actemra) target: IL-6 receptor
- Siltuximab (Sylvant) target: IL-6

- These are large molecules which probably do not cross the blood brain barrier. Are they relevant?

OTHER MECHANISMS

- Antioxiants
  - Ebselen
    - Acts as a lithium- mimetic through its ability to inhibit inositol monophosphatase (IMPase)
  - N-acetyl cysteine
  - L-carnosine
- Nicotinergics
  - Nicotine
  - Varenicline
- COMT inhibitor
  - Entacapone

NOT ONLY INFLAMMATION

- SMRI funded much of the early research on glutamatergic agents, such as glycine, and D-serine.
- Compounds from this group were later developed by Eli Lilly and Roche (unfortunately unsuccessfully...)
- Diabetes drugs (insulin might effect cognition)
  - exenatide
  - metformin
- buspirone

OTHER COMPOUNDS

- Estrogen and Raloxifene
- Omega-3 for the prodrome
- Folate for depression and negative symptoms
- Mirtazapine for negative symptoms
- Oxytocin for social functioning and negative symptoms
- SMRI is also testing a Jansenn nicotinic modulator for depression in an attempt to utilize drugs developed, and then shelved by pharma
- No invest in compounds heavily funded by others (ie NIMH funding of ketamine)

THOMSON REUTERS LIFE SCIENCES PROPOSAL FOR SUPPORT WITH DRUG REPOSITIONING FOR SCHIZOPHRENIA

Stanley Medical Research Institute / Tel-Aviv University
Sackler Faculty of Medicine

- Attempt to identify all medications, regardless of indication, which cross the blood brain barrier, and contemplate which to study
  - We approached a few companies with large medications databases and got access for a period of three months to the Thomson Reuters database, with the aim of finding medications that cross the blood brain barrier, and analyzing their potential use in schizophrenia.
  - The database did not have a tool for selecting medications that cross the blood brain barrier

SMALL SINGLE SITE STUDIES

- Typically SMRI will fund a small (N=60-80) single site study by an intellectually invested investigator with an idea.
- If 1-2 of these small studies are positive → SMRI will fund a larger more definitive study but a different PI (Omega 3, Aspirin)
- Question: what if one of these small studies shows a trend for improvement with drug which is not statistically significant?
  - Retested with larger sample size
  - Leave alone
  - Meta-analysis

SINGLE SITE STUDIES

- Many times single-site studies performed by an enthusiastic, intellectually invested researcher will be positive. Attempts at replication by non-invested researchers fail. How should this be addressed?
- How to deal with power issues?
- How to interpret small n negative finding studies?
- Should we fund only larger (N>200) studies?
  - These studies tend to be more expensive

HOW TO CHOOSE WHICH STUDY TO FUND

- SMRI has allowed itself over the years to fund original thinking at the expense of being politically correct.
- Some studies are the first to be tried in schizophrenia, so no previous experience on which to build, and not possible to do meta-analyses or how to estimate power
- Other studies are on compounds on which there are published data, but how do we know about unpublished negative findings?
  - Example: "Rumor has it" that Pfizer funded a large study on celocoxib that was negative, but not published.

USING CLINICAL DATABASES

- Assemble a very large clinical database of patients with schizophrenia (tens of thousands), with data on all medications (blood pressure, arthritis, heart disease, infections, etc).
- This large database could be used to determine if any of the non-psychiatric medications predict better or worse outcomes (hospitalizations, antipsychotic doses, etc.)
- Compounds associated with better outcomes might then be considered for RCTs.
- Such initiatives have been successful in cancer and cardiovascular research.

Non-steroidal anti-inflammatory drugs and the risk of psychosis

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Abstract The objective of the current research was to examine the relation between non-steroidal anti-inflammatory drugs (NSAID) use and risk of psychosis. To this end we performed a longitudinal case-control study using prescription data from a Dutch health insurance company. Men aged 25 years or over and women aged 30 years or over were excluded to prevent inclusion of non-incident cases. This resulted in eighty-two cases and 359 randomly selected controls from the same population. The overall relative risk of incident antipsychotic use for NSAID users, adjusted for age and prescription frequency, was 0.80 (95% CI: 0.48–1.33). After stratification for gender the risk of psychosis was significantly lower (59%) in male NSAID users only. The relative risks for male and female subjects were 0.41 (95% CI: 0.17–0.97) and 1.31 (95% CI: 0.65–2.64), respectively. These results suggest that in men NSAIDs may lower the risk of psychosis.

SUMMARY

- Repositioning studies funded by SMRI have made a major contribution to drug development in schizophrenia
- Performed groundwork for industry
- Inflammatory hypotheses are now widely considered in psychiatry

But still much work to be done!

Thank you Mr. Stanley!