Futility studies: Spending a little to save a lot

Phase II futility trial designs considered by Tilley et al. may decrease time to identify agents unworthy of further study and reduce subject exposure to ineffective futile treatments. Futility trials depend on clinically relevant or historically derived references to assess futility. Failure to find futility does not imply efficacy.

see page 628

Efficient phase II clinical trial design for ALS

Levy et al. describe the design of the Clinical Trial of High Dose Coenzyme Q10 in ALS (QALS study). A selection procedure to identify a preferred dose and a futility analysis reduce sample size and trial duration.

see page 660

Creatine and minocycline in early PD

The National Institute of Neurologic Disorders and Stroke (NET-PD) investigators conducted a futility trial of creatine and minocycline in early PD. The goal was to test whether these drugs altered the course of early PD relative to a threshold for progression derived from historical data. Both creatine and minocycline slowed disease progression relative to the futility threshold, suggesting that they merit further clinical study.

see page 664

The editorial by Schwid and Cutter about these three articles notes that Phase III studies require hundreds of patients to be followed for at least 2 years and cost millions of dollars. Preliminary evidence that a treatment is safe and likely to be helpful is essential before making such a large investment of human resources. Futility studies identify agents unlikely to demonstrate benefit rather than identifying the most promising agents. The big advantage of the futility design is that it allows some agents to be weeded out at the preliminary study stage while requiring a fraction of the patients and resources of more conventional efficacy studies. However, non-futile agents are less likely to show benefit in Phase III trials than agents demonstrating preliminary evidence of efficacy, unless futility thresholds are set stringently. After decades with little to offer patients with neurodegenerative diseases, being forced to choose between non-futile treatments to pursue in additional studies is a good problem to have.

see page 626

Neuropsychological deficits in long-term cannabis users

Messinis et al. studied neuropsychological functioning in long-term, heavy cannabis users (15.9 years) and found deficits on verbal fluency, memory, attention, and psychomotor speed compared to shorter term users (6.95 years).

see page 737

Recurrent stroke and cardiac risks after stroke

Dhamoon et al. followed 655 patients after their first ischemic stroke for up to 5 years. The risk of fatal cardiac events was almost twice that of fatal stroke, although risk of all recurrent strokes was approximately twice overall cardiac risk.

see page 641

Early interferon β -1a treatment more effective

Immediate Treatment Group														
Number at risk	100	95	89	86	84	81	77	74	69	66	53	31	17	4
Clinically definite MS	5	6	3	2	3	4	3	5	3	3	2	2	0	0
Early withdrawal	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Censor	0	0	0	0	0	0	0	0	0	10	20	12	13	4

Delayed Treatment Group														
Number at risk	103	93	88	77	72	68	65	62	58	55	40	20	4	0
Clinically definite MS	10	5	11	5	4	3	3	4	3	3	4	1	0	0
Early withdrawal	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Censor	0	0	0	0	0	0	0	0	0	12	15	14	4	0

Development rate of clinically definite MS.

In the CHAMPIONS study, treatment with interferon β -1a IM once weekly immediately following a first clinical demyelinating event delayed the rate of development of MS by 35% after 5 years compared to delayed initiation of therapy.

see page 678

Thrombolysis in pregnant women

Murugappan et al. treated eight pregnant women with stroke with thrombolytics. Seven recovered, but three were therapeutically aborted, while two miscarried. Two delivered healthy babies. Pregnant women may be given thrombolytics safely but risks/benefits to mother/fetus must be carefully weighed.

see page 768

The natural history of primary lateral sclerosis

Estimated survival function (with 95% confidence band) of time to diagnosis of upper motor neuron dominant (UMN-D) ALS.

Gordon et al. studied 39 patients diagnosed with PLS. Those with no lower motor neuron (LMN) signs 4 years after onset progressed slowly and maintained function. If LMN signs appeared within 4 years, disability was greater. The diagnosis of PLS is more secure after 4 years.

see page 647

The editorial by Rosenfeld and Swash notes that Gordon et al. have initiated a critical process of categorizing subgroups of patients with ALS by addressing a relatively easily identified population of patients with PLS. They suggest that this is one of many steps to categorize other ALS subgroups: indolent forms of motor neuron disease, rapidly aggressive forms, focal or monomelic forms, lower motor neuron-predominant presentations, ALS-FTD, generalized motor neuron degeneration, and asymmetric or multifocal forms of motor neuron degeneration. The search for environmental triggers and for treatment demands such a strategy.

see page 624

Patent foramen ovale, migraine, and stroke

Anzola et al. quantitated the right to left shunt from a patent foramen ovale in 420 consecutive patients with migraine, cryptogenic stroke, or neither condition and found that the patients with migraine and stroke had the largest shunt vs either migraine or stroke alone.

see page 765

Haptoglobin as a risk factor for cerebral artery vasospasm

Borsody et al. evaluated the relationship between the type of haptoglobin expressed by patients with subarachnoid hemorrhage and the development of cerebral artery vasospasm. Patients who expressed haptoglobins containing the α_2 subunit appeared to have a higher rate of vasospasm than did other patients.

see page 634

Cerebrovascular reactivity and subarachnoid hemorrhage

Frontera et al. found that in patients with acute subarachnoid hemorrhage, impending symptomatic vasospasm correlated with the appearance of abnormal cerebral vasoreactivity using transcranial Doppler and CO_2 inhalation.

see page 727

The editorial by Alejandro A. Rabinstein about these two articles notes that differentiation of vasospasm from other complications of SAH—hydrocephalus, cerebral edema, aneurysmal rebleeding, and hyponatremia—may be difficult. The amount of blood in the SA space on initial CT, young age, and history of smoking are risk factors, but their predictive value is limited. Both Neurology studies tested novel, simple tools for prediction and diagnosis of vasospasm. The Borsody et al. study needs to be confirmed in a larger cohort that incorporates clinical outcome measures (such as symptomatic vasospasm) and assessment of cognitive and functional status but suggests that haptoglobin typing may be clinically useful. The finding that abnormal CO_2 reactivity was significantly associated with the occurrence of symptomatic vasospasm could reflect abnormal vasomotor reactivity that is a nonspecific risk factor for neurologic decline. However, disturbed microcirculatory function identifiable by abnormal responses to CO_2 exposure could be responsible for this subcortical ischemia and represent a target for future therapeutic strategies.

see page 622

Memory impairment in now abstinent MDMA users and continued users

Zakzanis and Campbell investigated the functional consequences of continued neurotoxicity of ($\pm$)3, 4-methylenedioxymethamphetamine (MDMA) use in longitudinal follow-up. Current users demonstrated further decline in memory ability while former users improved or remained static on memory measures.

see page 740

Neurology®

March 14 Highlights

Neurology 2006;66;620-621

DOI 10.1212/01.wnl.0000207617.09966.88

This information is current as of March 13, 2006

Updated Information & Services

including high resolution figures, can be found at:
<http://n.neurology.org/content/66/5/620.full>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints

Information about ordering reprints can be found online:
<http://n.neurology.org/subscribers/advertise>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright . All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.