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Neuromyelitis Optica – Is there a Standard of Care?

EMA Workshop on NMO
London, October 10, 2014

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Immunosuppressive Therapy in NMO

Standard of Care?

Or

Available, empiric, unproven therapy based on the lowest level of evidence?

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"The term **Standard of Care** is now used so freely in everyday medical discussion"

Dirk C. Strauss and J. Meirion Thomas - Journal of Clinical Oncology, Vol 27, No 32 (November 10), 2009: pp e192-e193

What does it mean?

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Standard of Care – Legal Perspective

- **Legal Definition:** "The caution that a reasonable person in similar circumstances would exercise in providing care to a patient."
- *Daubert v. Merrell Dow Inc.* (U.S. Supreme Court, 1993), to admit into evidence scientific testimony as "expert testimony," the testimony must **constitute valid scientific knowledge**:
  - Can the theory or technique be subject to **empirical testing?**
  - Has the idea been subject to **peer review** or published in scientific journals?
  - Is the theory or technique **generally accepted** by the relevant scientific community?

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Dirk C. Strauss and J. Meirion Thomas -Journal of Clinical Oncology, Vol 27, No 32 (November 10), 2009: pp e192-e193

Standard of Care – Medical Perspective

- NIH Consensus Development Program:
  - "Consensus statements should represent views from a broad-based, nonadvocating, balanced, and objective panel of experts."
  - "This further prevents investigations or treatment **being declared standard of care based on single studies, often not representing the best or highest level of evidence"**
- Difficulty inherent in guidelines that are based in part on consensus: **biases of the experts may shape the guideline.**
- **"**Modern and scientific healthcare should be firmly set in evidence-based medicine. Therefore the term standard of care should be used with caution**."** [Sackett DL, Rosenberg WM, Gray JA, et al: Evidence-based medicine: What it is and what it isn't. BMJ 312:71-72, 1996]
- Perhaps the term "standard of care" should not be used **unless supported by confirmatory randomized controlled trials or meta-analysis that are unchallenged**

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Dirk C. Strauss and J. Meirion Thomas -Journal of Clinical Oncology, Vol 27, No 32 (November 10), 2009: pp e192-e193

"Various immunosuppressive agents (e.g. azathioprine, mycophenolate mofetil, rituximab, and corticosteroids) are prescribed to reduce attack frequency based on results of small prospective and retrospective uncontrolled studies. These agents are collectively **referred to as "empiric" treatments** in this paper to **avoid suggesting that a standard of NMO therapy has been established.**"

Challenges and Opportunities in Designing Clinical Trials for Neuromyelitis Optica.
Brian G. Weinshenker and multiple authors on behalf of The Guthy–Jackson Charitable Foundation International Clinical Consortium – Submitted for publication

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EFNS guidelines on diagnosis and management of Neuromyelitis Optica

- "There are **no randomized-controlled** trials and currently **only class IV evidence** for effect of any medication for relapse prevention."
- "Hence, data favoring specific therapies **are weak**. Immunosuppression is the preferred treatment, but optimal drug regime and treatment duration are **yet to be determined."**

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J. Sellner et al-European Journal of Neurology 2010

American Academy of Neurology (AAN) - Clinical Practice Guidelines

Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a–e Class I, above, or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e Class I, above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

AAN classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

NMO

Adapted from: Gross R; Levels of evidence: Taking Neurology to the next level. *Neurology* 2009;72;8-10.

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Level of Evidence and Clinical Equipoise

- **Clinical equipoise:** Ethical concept that reconciles broader social interests with the obligations of physicians and the rights of patients.
- **Requires:** At start of a clinical study must be a state of **reasonable, professional disagreement** among members of the relevant expert community.
- Because of society's interest in medical treatment resting on high quality evidence, **lack of evidence can be grounds for reasonable professional disagreement**

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Sheehan M, et al. J Med Ethics 2013;0:1–4. doi:10.1136/medethics-2012-101290

WMA Declaration of Helsinki
#33 - October 2013

Use of placebo appropriate in the following circumstances:

- Where **no proven intervention exists;**
- Where for compelling and scientifically sound methodological reasons, the use of any intervention less effective than the best **proven** one **is necessary to determine the efficacy and safety of an intervention;**
- And the **patients** who receive any intervention less effective than the best proven one **will not be subject to additional risks of serious or irreversible harm** as a result of not receiving the best **proven intervention**.

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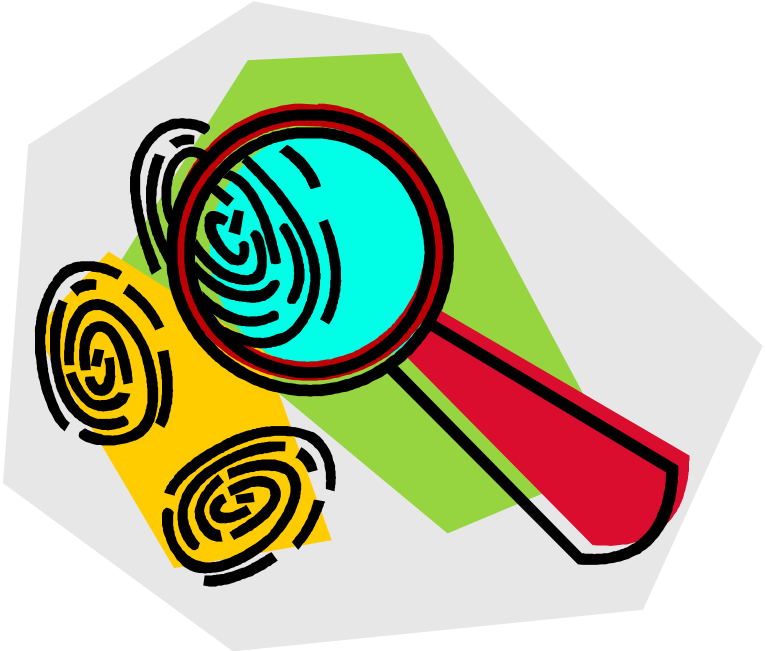
“There is no place in science for consensus or opinion, only evidence.”

Claude Bernard



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Do any of the treatments currently used for relapse prevention in NMO, constitute valid, proven, scientific knowledge, based on a high level of evidence??

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CTI CLINICAL TRIAL & CONSULTING

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A Systematic Review of the Literature

- Review performed in compliance with MOOSE and PRISMA guidelines for systematic review research
- MEDLINE, Embase, Cochrane data bases were used. Included all publications before January 31, 2014.

Systematic Literature Review Funnel Diagram

2,438 initial citations identified

105 accepted studies reporting results from NMO therapies

Acute Treatment

- 34 studies – steroids
- 14 studies – plasma exchange

Maintenance Therapy

- 1 study – steroids
- 6 studies – azathioprine ± steroids
- 5 studies – cyclophosphamide ± steroids
- 2 studies – methotrexate ± steroids
- 5 studies – mitoxantrone ± steroids
- 4 studies – IV IgG
- 7 studies – rituximab
- 8 studies – miscellaneous immunomodulatory agents
- 11 studies – interferon

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Characteristics of this Systematic Review

- **Majority of published studies: small, observational studies.**
- **In absence of controlled trial, the observed downward change in ARR or EDSS may be due to treatment effect or regression toward mean and/or the selection bias of the cohort being studied**
- **Accepted observational studies rarely included sufficient methodology details to evaluate selection and information bias and confounding factors.**
- **Benefit/risk assessment for maintenance therapies could not be determined due to minimal publication of safety evaluations**
- **Level of evidence for therapeutic studies was classified based on the AAN classification of Levels I, II, III, and IV.**

French and Gronseth. Neurology: 2008 Nov 11;71(20):1634-8

Systematic Literature Review

RESULTS

Summary of Studies of Azathioprine ± Steroids for Preventing Relapses of NMO/NMOSD

Author, Year	Evid. Level	Treatment	Regimen	# Pts	Mean ± SD or Median (range) ARR pre→post treatment	Mean ± SD or Median (range) EDSS pre→post treatment	Other effects
Bichuetti et al 2010	4 (CS)	azathioprine + prednisone	150 mg PO qd 5-60 mg PO qd	7	5.0 ± 2.9 → 1.0 ± 1.8 (p<0.001)	4.7 ± 2.2 → 4.7 ± 2.2	
Costanzi et al 2011	4 (CS)	azathioprine ± prednisone	NR; 1-180 mo 20-80 mg PO qd	70	2.18 → 0.64 (p<0.0001)	3.5 (0-8.5) → 3.5 (1.0-8.5)	35% (25/70) stopped treatment for side effects
Kageyama et al 2013	4 (CS)	azathioprine + prednisone	100 mg PO qd, 35-55 mo 6-10 mg PO qd	9	1.7 (1.2-2.7) → 0.47 (0.36-0.59) (p=0.028)	3.5 (3.5-5.5) →	
Mandler et al 1998	4 (CS)	Methyl-prednisolone + prednisone + azathioprine	1 g IV qdx5 1 mg/kg PO qdx60 from d6 2 mg/kg PO qd from d21	7			
Sahraian et al 2010	4 (CS)	azathioprine	200 mg PO qd, 17 ± 28 mo	28	0.99 → 0.40		
Elsone et al 2014	4 (CS)	azathioprine ± prednisone	25 mg increased 2.5-3mg/kg daily	103	1.5→0 (p<0.00005)	6 → 5	
Mealy et al 2014	4 (CS)	azathioprine, rituximab, or MMF	2 to 3 mg/kg/d	90	2.26→0.63 (p=0.004) 2.89→0.33 2.61→0.33		risk of relapse 2-fold higher on azathioprine compared with rituximab

- 6/7 studies reported reduction in ARR

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CS: case series; NR: not reported; PCS: prospective cohort study; RCS: retrospective cohort study; RCT: randomized controlled trial; SD: standard deviation; SQ:subcutaneous

Large Multi-Center Retrospective Case Studies of Azathioprine ± Steroids

- **Costanzi et al,** ***2011 Neurology; 77:659-666***
  - 70 patients treated with azathioprine **1994–2009 (15 years)**
  - Thirty-eight patients **(54%)** discontinued drug (side effects, 22; no efficacy, 13; lymphoma,3)
  - 66% patients experienced relapse
  - statistically significant reduction in mean ARR ($p<0.0001$),

- **Elsone et al,** ***2014, Multiple Sclerosis Journal***
  - 103 patients who received azathioprine + prednisone, at any time
  - treatment was discontinued in 46% (n = 47). 62% (n = 29) side effects, 19% (n = 9) death, 15% (n = 7) ongoing disease activity, and 2% (n = 1) pregnancy
  - significant reduction in mean ARR
  - **9 patients died**. Treatment related? 3 pneumonia, 1 sepsis, 4 unknown, 1 Heart failure

- **Mealy et al,** ***2014,JAMA Neurology; 71, (3)***
  - 90 patients over 10 years period
  - “there is no consensus on how to select initial therapy”
  - azathioprine (n=32), rituximab (n=30), mycophenolate mofetil (n=28).
  - All treatments: significant reduction in ARR
  - Variety of treatment prior to initiation of one of three drugs.
  - No safety data.
  - “This study is limited by the biases inherent to retrospective study design”

Summary of Studies of Rituximab for Preventing Relapses of NMO/NMOSD

Author, Year	Evid. Level	Treatment	Regimen	# Pts	Mean ± SD or Median (range) ARR pre→post treatment	Mean ± SD or Median (range) EDSS pre→post treatment
Bedi et al 2011	4 (CS)	methylprednisolone + rituximab	1g IV qdx10 (acute attacks) 1g IV biweekly q6m	23	1.87 (0.31-5.14) → 0.0 (0.0-1.33; p<0.01)	7.0 (3.0-9.0) → 5.5 (0.0-8.0; p<0.02)
Bomprezzi et al 2011	4 (CS)	methylprednisolone ± plasma exchange + rituximab	1g IV qdx5 (acute attacks) 1 g IV q2w x2, repeat when CD27+ >1% PBMCs	18	1.17 → 0.06	
Gredler et al 2013	4 (CS)	rituximab	375 mg/m^2 IV q2-6m x3-16	4	2.8 (2.25-3.0) → 0.4 (0.0-0.83; p<0.05)	5.3 (3.0-7.5) → 3.3 (1.0-7.5)
Ip et al 2012	4 (CS)	methylprednisolone + immunoglobulin + rituximab	0.5-1g IV qd, d1-5 (acute) 0.4 g/kg IV qd d5-10 1 g IV biweekly q6-9m	7	2 (1-4) → 0 (5/7 relapse free over 24 mo)	8.0 (6.9-9.5) → 7.0 (3.0-9.5)
Jacob et al 2008	4 (CS)	rituximab	375 mg/m^2 IV qwx4,q6-9m	25	1.7 (0.5-5.0) → 0.0 (0.0-3.2; p<0.001)	7.0 (3.0-9.5) → 5.0 (3.0-10.0; p=0.02)
Jarius et al 2008	4 (CS)	rituximab	375 mg/m^2 IV qwx4,q6-9m	4	2.3 (1.55-2.79) → 0.51 (0.46-1.04)	
Kim et al 2011	4 (CS)	rituximab	375 mg/m^2 IV qwx4, repeat when CD27+ >0.05% PBMCs	30	2.4 (0.4-8.0)→ 0.3 (0.0-4.0)	4.4 (1.0-8.5) → 3.0 (1.0-7.5; p<0.001)
Lindsey et al 2012	4 (CS)	rit				0) → 0.0)
Pellkofer et al 2011	4 (CS)	rit				5) → 3.0)
Yang et al 2013	4 (CS)	ritux	CD27+ >1% PBMCs		0.0 (0.0-0.0)	.0) → 5.0 (2.5-8.0)

- 10 case studies for NMO maintenance
- 9/10 studies reported a marked reduction in mean ARR
- 7/8 studies reporting treatment effects on EDSS

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CS: case series; NR: not reported; PCS: prospective cohort study; RCS: retrospective cohort study; RCT: randomized controlled trial; SD: standard deviation; SQ:subcutaneous

Summary of Studies of Cylophosphamide ± Steroids

- 3 small case studies for NMO maintenance
- 2 studies showed improvement in neurologic function
- 1 study showed cyclophosphamide to be ineffective and toxic
- **Level 4 evidence**

Summary of Studies of Methotrexate ± Steroids

- 2 small case studies for NMO maintenance
- Both studies reported disease stabilizations on low-dose methotrexate treatment
- **Level 4 evidence**

Summary of Studies of Mitoxantrone ± Steroids

- 3 case studies for NMO maintenance
- All studies reported marked reduction in ARR and disease burden (ie, lowered EDSS scores)
- **Level 4 evidence**

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CS: case series; NR: not reported; PCS: prospective cohort study; RCS: retrospective cohort study; RCT: randomized controlled trial; SD: standard deviation; SQ:subcutaneous

Summary of Studies of Miscellaneous Agents ± Steroids for Preventing Relapses of NMO/NMOSD

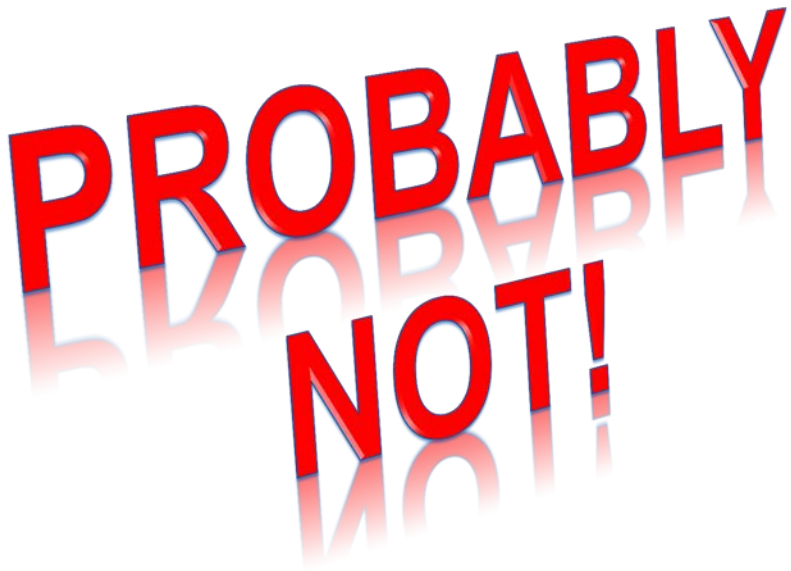
Author, Year	Evid. Level	Treatment	Regimen	# Pts	Mean ± SD or Median (range) ARR pre→post treatment	Mean ± SD or Median (range) EDSS pre→post treatment
Jacob et al 2009	4 (CS)	mycophenolate mofetil	2000 mg PO qd median 27 (1-89) mo	24	1.28 (0.23-11.78) → 0.09 (0.0-1.56; p<0.001)	6.0 (0.0-8.0) → 5.5 (0.0-10.0)
Sahraian et al 2010	4 (CS)	mycophenolate mofetil	1500-2000 mg PO qd median 4 mo	6	0/6 relapsed over median 4mo treatment	
Bichuetti et al 2013	4 (CS)	IVIg	0.4 g/kg IV qdx5, q2m (2-10 cycles)	8	1.8 ± 1.6 → 0.1 ± 0.2	
Magraner et al 2013	4 (CS)	IVIg	0.7 g/kg IV qdx3, q2m (4-21 infusions)	8	1.8 → 0.006 (p=0.01)	3.3 ± 1.3 → 2.6 ± 1.5 (p=0.04)
Pittock et al 2013	4 (CS)	eculizumab	600 mg IV qw w1-4, 900 mg IV q2w for 48wk	14	3 (2.0-4.0) → 0 (0-1.0; p<0.0001)	4.3 (1.0-8.0) → 3.5 (0.0-8.0; p=0.0078)
Kleiter et al 2012	4 (CS)	natalizumab	median of 8 (2-11) monthly infusions	5	3.2 (3.0-4.0) → 1.4 (1.0-3.0)	4.0 (1.0-7.5) → 5.8 (1.5-9.0)
Kageyama et al 2013	4 (CS)	cyclosporine A + prednisone	150 mg PO qd for 31 mo 6-10 mg PO qd	9	2.7 (1.8-4.3) → 0.38 (0.0-0.97; p=0.012)	6.5 (2.0-7.5) → 3.5 (2.0-6.5)
Feng et al 2010	3 (PCS)	antituberculosis tx: isoniazid + rifampicin + pyrazinamide + streptomycin	8 mg/kg PO qd x24m 10 mg/kg PO qd x24m 25 mg/kg PO qd x6m 20 mg/kg PO qd x2m	12		
Xu et al 2011	4 (CS)	autologous stem cell transplant		21		
Lu et al 2012	4 (CS)	human umbilical cord mesenchymal stem cell therapy		5	(p<0.05)	

- 10 small case studies reported on 8 additional agents
- Majority showed reduction in mean ARR and EDSS

Inherent faults in existing studies *(in addition to their all being retrospective case studies with no comparator)*

- AQP4-IgG discovered in 2004:
  - Different patient population before and after
  - Time for adaptation of assay for routine clinical use
  - Different and non-standardized methodology
- Revised NMO diagnostic criteria published in 2006
  - Different patient population before and after
- No unified accepted definition of NMO relapse
- No safety data reported in most studies
- Dose regimens and length of therapy differ largely within studies and between studies

Do <u>any</u> of the treatments currently used for relapse prevention in NMO constitute valid, proven, scientific knowledge based on high level of evidence??



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Recent Published NMO Treatment Guidelines – "SOC"?

"Therefore the term standard of care should be used with caution. Currently, it can be self-awarded either by a group of like-minded individuals or by a specialist society or organization and is a term which can be abused with the intention of providing impact and authenticity to a point of view."

Dirk C. Strauss and J. Meirion Thomas -Journal of Clinical Oncology, Vol 27, No 32 (November 10), 2009: pp e192-e193

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Published Guidelines for Relapse Prevention in NMO

First Line Therapy

- **European Federation of Neurological Societies (EFNS)**
  Based on 1 case series (n=7, azathioprine; n=25, rituximab)

- **Neuromyelitis Optica Study Group (NEMOS,Germany)**
  Azathioprine- based on 3 case series (n=7, n=70, n=3)

  Rituximab- based on 5 case series (n=23, n=25, n= 4, n=30, n=10)

- **Guthy Jackson Charitable Foundation Clinical Consortium and Biorepository (GJCF-CC&BR)**

  Azathioprine- based on 5 case series (n=7, n=70, n=7, n=10, n=28)

  Rituximab- based on 5 case series (n=23, n=25, n=30, n=8, n=10)

- **The American Academy of Neurology Subcommittee**

  Rituximab-based on 1 case study (n=25) and kin study (n=8), for TM in NMO

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Treatment Guidelines for Maintenance Therapy of NMO/NMOSD

- **All meet class U per AAN Criteria**
  - **Data inadequate or conflicting; given current knowledge, treatment is unproven.**
- Evidence is probably not sufficient as a basis for treatment guidelines.

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Anti-Arrhythmia Treatment Post Acute MI – SOC or….NOT?

Effects of Encainide, Flecainide, Imipramine and Moricizine on Ventricular Arrhythmias During the Year After Acute Myocardial Infarction: *THE CARDIAC ARRHYTHMIA PILOT STUDY (CAPS)*

As first drugs, encainide and flecainide had higher efficacy rates, 79% and 83 % , respectively. Encainide, flecainide and moricizine were well tolerated. These 3 drugs had intolerable adverse effect rates of 6% or less.

MORTALITY AND MORBIDITY IN PATIENTS RECEIVING ENCAINIDE, FLECAINIDE, OR PLACEBO

The Cardiac Arrhythmia Suppression Trial

"There was an excess of death due to arrhythmia and death due to shock after acute recurrent myocardial infarction in patients treated with encainide or flecainide"

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Menopausal Hormone Therapy: SOC or…. NOT?

Menopausal Hormone Therapy

ONCE: Use of hormone therapy to ward off heart disease, osteoporosis, and cancer, while improving women's quality of life.

BUT: July 2002, findings emerged: long-term use of hormone therapy *poses serious risks and may increase the risk of heart attack and stroke.*

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Heart, Lung, and Blood Institute

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Immunosuppressive Therapy in NMO

Is

An available, empiric, unproven therapy based on the lowest level of evidence.

And probably should not be labeled as "Standard of Care"

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Thank You !!!!