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Women's Issues in Epilepsy

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How are women different?

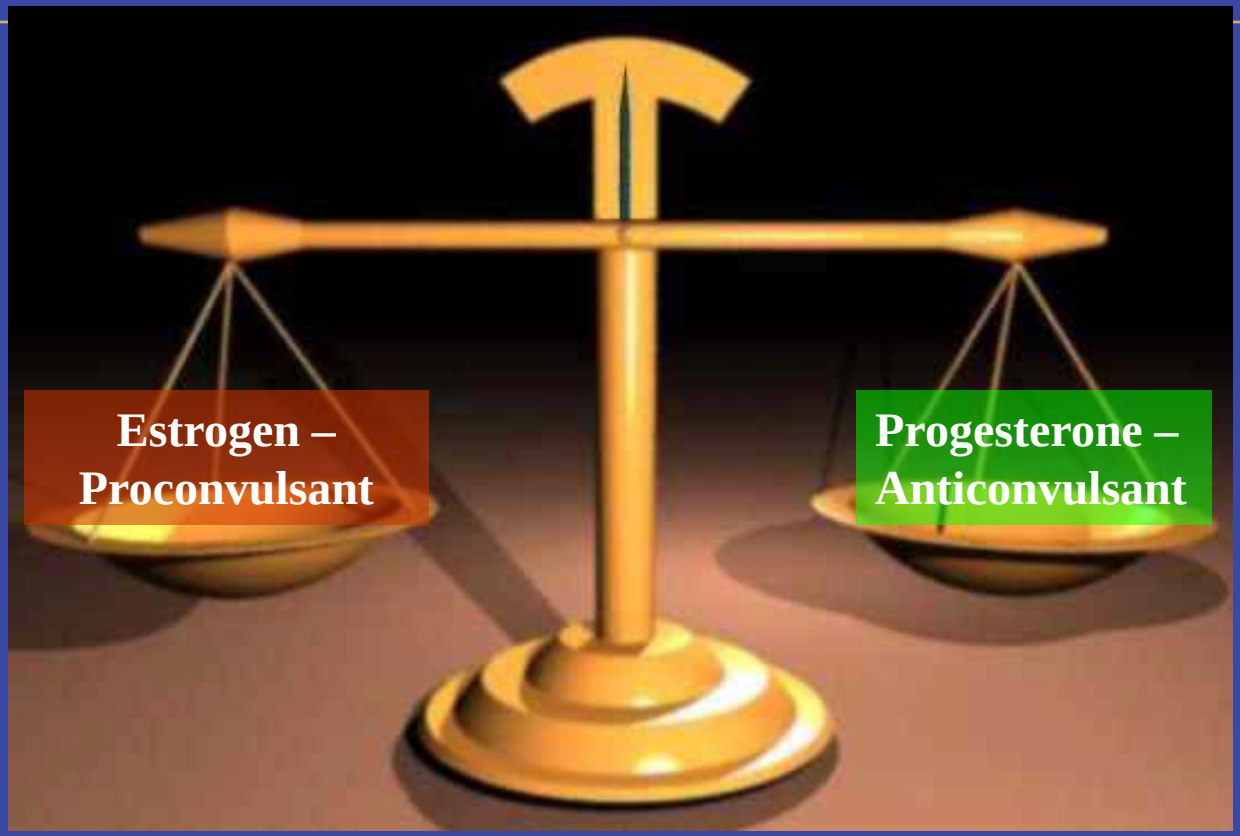
- Different habitus
- Different metabolism
- Different co-morbidities
- Different psychosocial stigma
- Different hormonal status
  - Catamenial seizures
  - Pregnancy
  - Menopause

Hormones and Epilepsy

- Estradiol
  - exerts direct excitatory effects at the neuronal membrane by augments N methyl-D-aspartate (NMDA) mediated glutamate receptor activity
  - decreases inhibition by decreasing GABA synthesis
  - Logothetis et al. showed that intravenously administered conjugated estrogen activated epileptiform activity in 11/16 women, and associated with seizures in 4

Hormones and Epilepsy

- Progesterone
  - progesterone, especially its neuroactive metabolite (allopregnanolone) exert direct membrane-mediated inhibitory effects by potentiating GABA A-mediated chloride conductance
  - also potentiates the action of the powerful endogenous inhibitory substance adenosine
  - Backstrom et al. found that iv progesterone at sufficient doses was associated with decrease interictal spikes in 4/7 women with partial epilepsy


Estrogen –
Proconvulsant
Progesterone –
Anticonvulsant

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Epilepsy and Fertility Issues

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Epilepsy and Fertility

- Decreased fertility among women with epilepsy (II)
  - Polycystic Ovarian Disease
  - Sexual Dysfunction
  - Psychosocial effect of epilepsy
  - AED effect to the fetus
  - Effect of seizures for the fetus
- AED and OCP interactions

Polycystic Ovarian Disease (PCOS)

- Failure of the ovarian follicle to complete normal maturation during the menstrual cycle

- Syndrome of
  - hyperandrogenism (raised testosterone levels)
  - multiple ovarian cysts
  - anovulatory cycles
  - hirsutism
  - obesity

- Prevalence of PCOS
  - in women without epilepsy is between 4% -6%
  - in women with epilepsy unknown (~ 2 x that of women without epilepsy), even in those not taking AED medication*
  - more common in women taking valproate, especially if started < age 20

AEDs and OCPs

- Increased breakthrough bleeding noticed when dosing of OCP decreased from 50-100ug to < 50 ug (due to risk of thrombosis)

- Modern available combined OCPs contain 20–35 ug of ethinylestradiol and < 1 mg of progestogen

Effect of antiepileptic drugs (AEDs) on hormonal contraceptive agents[14]

Enzyme-inducing AEDs	Enzyme-inhibiting AEDs	AEDs with no effect
Barbiturates	Felbamate	Ethosuximide
Carbamazepine	Valproate	Gabapentin
Oxcarbazepine		Lamotrigine
Phenytoin		Levetiracetam
Topiramate >200 mg/day		Tiagabine
		Zonisamide

Lamotrigine*

- cOCP can decrease lamotrigine trough levels by 25–70% AND…
- 20% to 100% of progestogen-only oral contraceptive

Benzodiazepines

- no effect on OCP

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For women on enzyme-inducing AEDs wishing to take OCPs

- cOCP
  - Start with 50 μg/day ethinyl oestradiol dosage (C)
  - If breakthrough bleeding occurs, increase the dose of ethinyl oestradiol to 75 or 100 μg/day (C)
- Other contraceptive methods
  - Medroxyprogesterone injections effective (III) but take q10 weeks rather than 12 weeks if using enzyme-inducing AEDs
  - IUDs also effective (acts locally)
  - Emergency contraceptive pill can be used in women with epilepsy after unprotected sexual intercourse (C)
- Ineffective
  - Progesterone only pill (III)
  - Levonorgestrel implants - high failure rate (III)
- Should always recommend second contraceptive methods

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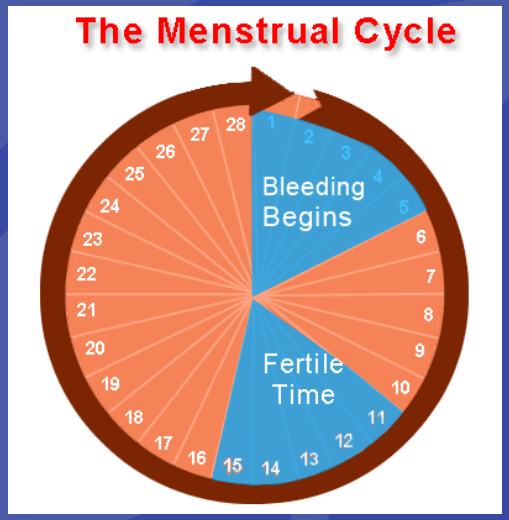

Catamenial Seizures

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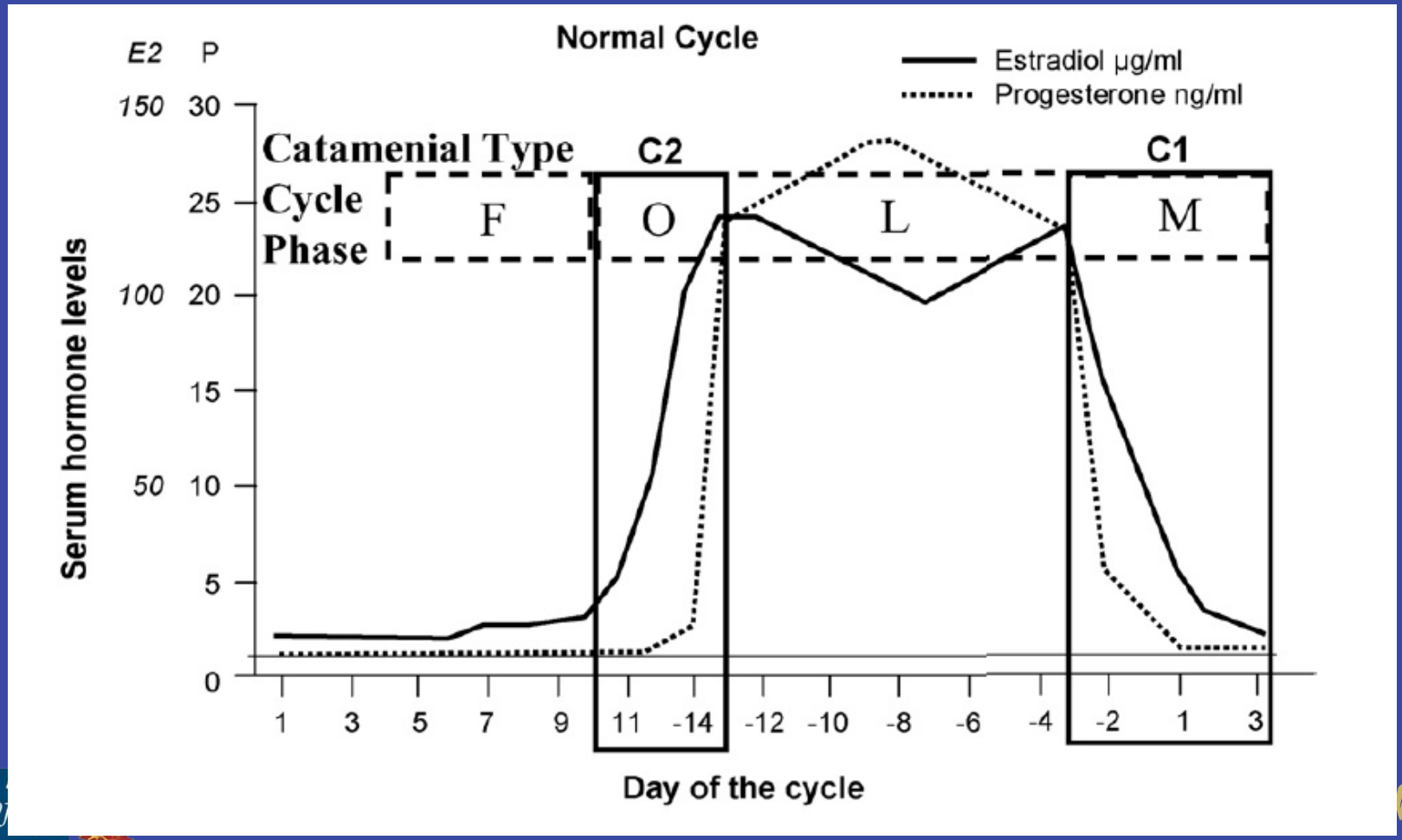
Catamenial Seizures

- Doubling of seizures around menses
- Occurs in about 12% of women with epilepsy (II)
- Can affect ~ 1/3 of women with localization-related epilepsy
- 3 catamenial seizure patterns have been identified
  - Ovulatory cycles
    - » During perimenstrual days (pattern C1)
    - » Periovulation (pattern C2)
  - Anovulatory cycles
    - » Post-ovulation, when luteal phase inadequate (pattern C3)

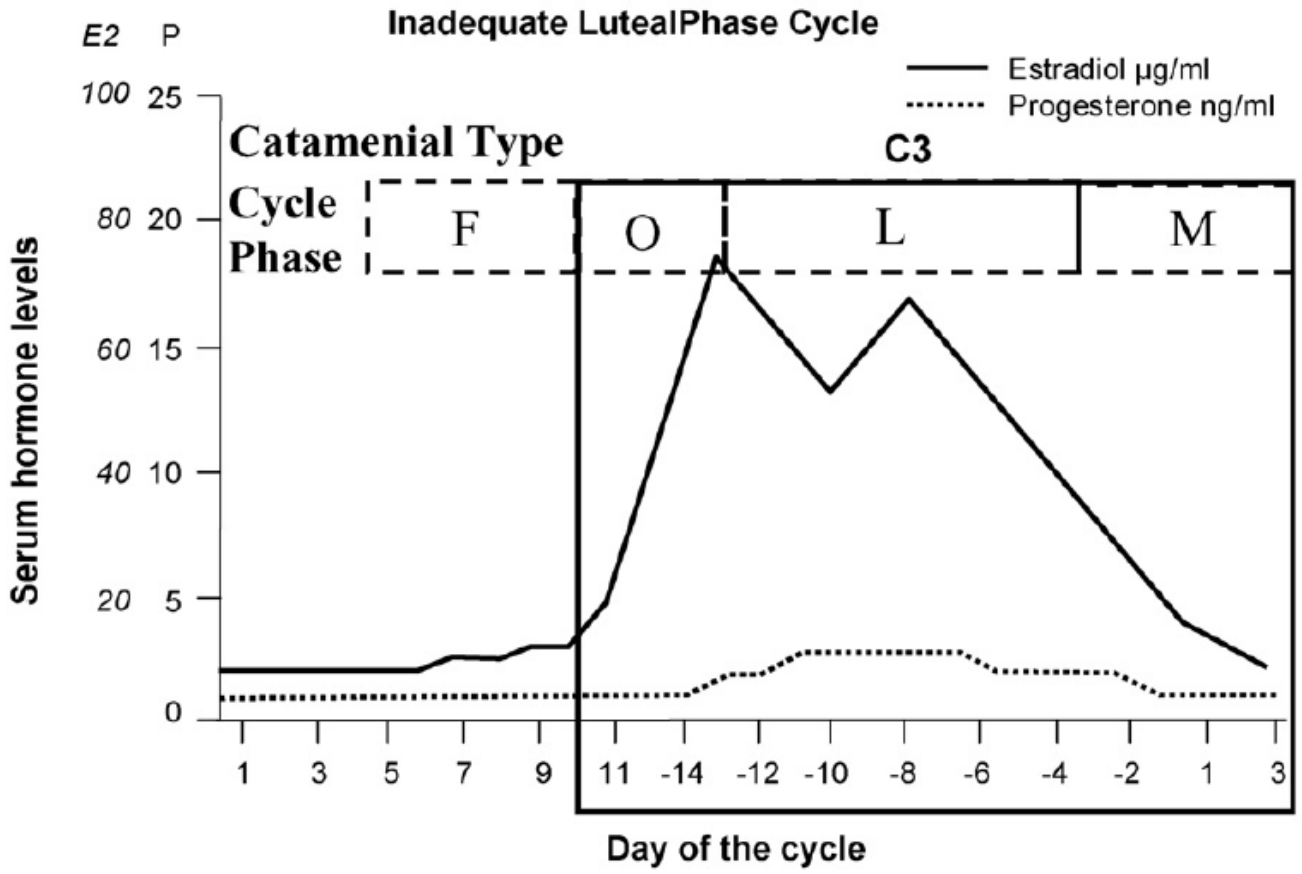
Ovulatory Cycles

- Seizure frequency shows positive correlation with serum estradiol/progesterone ratio
- Ratio is highest during days prior to ovulation and menstruation and is lowest during the early and midluteal phase (post-ovulatory)
- Premenstrual exacerbation of seizures has been attributed to the rapid withdrawal of the antiseizure effects of progesterone

Ovulatory Cycle



Anovulatory Cycle



Catamenial Seizures

- Catamenial seizure exacerbations primarily related to changing sex hormone concentrations during the menstrual cycle

- But also alterations in AED concentrations, as seen with phenytoin and lamotrigine, throughout the menstrual cycle

Catamenial Seizures – Treatment Strategies

- ↑ AED dose around time of ↑ seizures
- Avoid cyclic variation by a continuous OCP
- Supplemental progesterone during luteal phase
- Double-blind, randomized, placebo-controlled trial of cyclic supplemental progesterone currently underway

Catamenial Seizures – Treatment Strategies

- For women already on AEDs
  - intermittent clobazam on days when ↑ seizures (B)
  - acetazolamide perimenstrually (C)
  - progestogens perimenstrually (C)

- For women not already taking AEDs
  - intermittent perimenstrual clobazam (5 to 30 mg/day)
  - COCP; depot progestogen therapy; or perimenstrual progestogen (III)

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Pregnancy and Epilepsy

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Pregnancy and Epilepsy

- > 90% of women with epilepsy have a normal pregnancy
- Obstetrical risks of pregnancy inconclusive
  - low birth weight
  - preeclampsia
  - bleeding
  - placental abruption
  - prematurity
  - neonatal or perinatal death reported 2-3x higher, though wide variability in studies, including one study with no increased risk of death*
- No increased risk of major fetal malformation

Pregnancy and Epilepsy

- Most women will have no change of their seizure pattern during pregnancy (~50%), 25% will have improved seizure frequency

- Factors that may exacerbate seizures
  - noncompliance
  - nausea and vomitting
  - inappropriate decrease in AED
  - changes in blood volumes
  - sleep deprivation

- If a patient has been seizure free for at least 2– 3 years with no risk factors for seizure recurrence, consider withdrawing AEDs 6 months prior to planned conception

Pregnancy and Anticonvulsants

- Increased risk of fetal malformations with intrauterine exposure to 4 major anticonvulsants
  - Phenytoin
  - Carbemazepine
  - Valproic acid
  - Phenobarbital
- Major fetal malformations is 4-6% vs 2-3%
- Most studies identify valproate (~7-10%) or polytherapy (15%) exposure as the highest risk, especially in first trimester*

Pregnancy and Anticonvulsants

- Valproic Acid
  - 1-2% of babies with neural tube defects (10-20x)
  - Major birth defects in VPA monotherapy 10.7% vs 2.9% for other AEDs
  - Dose related
    - ≤1000 mg/day OR ~ 1
    - ≤1500 mg/day OR = 3.7
    - >1500 mg/day OR = 10.9*
- Lamotrigine
  - Best studied newer AED
  - ~3% incidence of major malformations with 1st trimester exposure
  - North American AED Pregnancy Registry noted a higher than expected prevalence of cleft palate and/or cleft lip (not reproduced)

Longterm effects of AED exposure

- Intrauterine exposure to valproate resulted in children with IQ scores ~ 6-9 points lower than those exposed to other AED (lamotrigine, phenytoin, or carbamazepine)

- No specific dose response established

Post-partum

- 1-2% of women with active epilepsy will have a tonic–clonic seizure during labor
- Further 1–2% will have a seizure within 24 h*
- If AED dose increased during pregnancy, gradually reduce it to preconception dose over the few weeks following delivery, to reduce the risk of maternal drug toxicity

Breastfeeding and AEDs

- Any theoretical risks need to be balanced against the known benefits of breastfeeding,
  - psychological benefits for mother and child
  - reduced infant mortality
  - fewer infectious disease
  - decreased risk of immunologically mediated disorders (type 1 DM)*
- Current recommendations all support breastfeeding
  - Watch for lethargy (especially with benzodiazepines, barbituates)
  - Lamotrigine
    - Increased risk of toxicity
    - Suggest lamotrigine levels should be monitored in breastfed children whose mothers are taking high-dose lamotrigine

Recommendations

- AED therapy should be optimized prior to conception (monotherapy preferred)
  - No agreement to which AED is most or least teratogenic
  - AED that stops seizures in a given patient is the one that should be used (VPA*)
  - Plasma drug level should be monitored regularly during pregnancy (free drug levels more reliable)
  - Screen for neural tube defects, specialized OB centre
- Folic acid daily prior to conception
- Vitamin K (20 mg/day po) in last month, infants should receive 1mg IM at birth
- Breast feeding recommending even while on AED

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Epilepsy and Menopause

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Epilepsy and Menopause

- Epilepsy can alter timing of menopause*
  - Association between partial epilepsy and premature menopause
  - Relationship between seizure frequency and age at menopause
  - Increased frequency of premature ovarian failure in women with epilepsy

Epilepsy and Menopause

- Small survey studies report ↑ seizures during the perimenopausal transition, but improved seizure frequency once menopause complete*
- Catamenial epilepsy pattern a hallmark for the observed increase at perimenopause but decrease at menopause
- Multicenter, randomized, placebo-controlled trial in postmenopausal women with epilepsy demonstrated ↑ seizure frequency in a dose-dependent fashion with HRT (Prempro, conjugated equine estrogens plus medroxyprogesterone acetate)*

Epilepsy and Menopause

- During menopause seizure frequency
  - Worsens in ~ 40%
  - Improves in ~30%
  - No change in ~ 30%*

- HRT significantly ↑ seizure frequency during menopause, more likely in women with history of catamenial epilepsy

Epilepsy and Bone Health

- Women with epilepsy at ↑ risk of fractures, osteoporosis, and osteomalacia
- ~10% of women with epilepsy have premature bone demineralization, especially if using AEDs that induce the hepatic cytochrome P450 enzyme system
- Multifactorial
  - Adverse effects of AEDs on bone metabolism, vitamin D, bone turnover
  - Trauma of seizures
  - Subtle effects of AEDs on coordination
- Most effective therapy for AED-induced osteoporosis has not been established

Risk factors for early osteopenia and secondary osteoporosis[24]

- Inadequate nutrition, especially deficient calcium intake
- Weight < 127 lb
- Inadequate weight-bearing exercise
- Neuromuscular impairment
- Institutionalized or wheelchair/bed-bound status
- Treatment with phenobarbital, primidone, phenytoin, carbamazepine*, or valproate*
- Smoking
- Excessive alcohol intake
- Prolonged steroid therapy
- Menopause
- Fair complexion, or Asian or northern European ancestry

* Studies are being completed.

Recommendations

- Screening with bone scans of the spine or hip should be obtained in at-risk women and be repeated every 2 years or if a fracture occurs
- Women should be counseled about adequate calcium intake, and a dietary history should be obtained
- Supplementation with calcium and vitamin D

Conclusions

- Women with epilepsy have unique issues
  - Fertility
  - Catamenial seizures
  - Pregnancy
  - Menopause
  - Bone Health

Thank you!

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