Recent Drug Therapy Issues

1. Androgens in the Aging Male

True Hypogonadism – Treat; PADAM – Caution

2. Topical Corticosteroids on the Face (Pg 3)

3. Adverse Reaction Reporting (Pg 4)

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Testosterone therapy in aging males has gained interest especially with advertising in the lay press and the resulting "pressure to prescribe". Advertising often focuses on "body image" rather than clinical issues. The term "andropause" is misleading as men, unlike women, do not have a total reduction in hormone levels; however, levels of testosterone do generally decline with age.[1] A more suitable term may be "partial androgen deficiency in the aging male" or **PADAM**. Symptoms overlap with age associated changes and other medical conditions (e.g. depression and hypothyroidism).

Table 1: Symptoms of Androgen Deficiency [2]

- ↓ sexual desire and erectile quality
- changes in mood (depression, fatigue)
- ↓ lean body mass, muscle & strength
- ↑ visceral fat
- alterations in skin and body hair
- ↓ bone mineral density

CAUTION required in distinguishing true hypogonadism from symptoms naturally occurring with age (often multifactorial).

As opposed to **true hypogonadism**, the decision to initiate androgen therapy in **PADAM** is subjective and controversial. Considerations include early morning testosterone levels (before ~9:30am) or preferably a 'free androgen index', severity of symptoms and a risk/benefit assessment. Testosterone levels have limitations given difficulties in interpretation and poor correlation between mildly low levels and symptoms.[3,4] Symptom screening tools alone may result in a false positive diagnosis (up to 40% with the Morley Questionnaire)[5,6]. A trial of at least 3-6 months is required to differentiate true benefits from placebo effects.[2] Long-term use depends on ongoing evaluation of clinical response, risk and assessment of testosterone levels.

Efficacy And Safety of Androgen Therapy in Aging Males
Small, short term trials and anecdotal reports have found androgens to have a variety of positive effects on mood, libido, strength and bone density.[1] Benefits are well accepted in symptomatic patients with hypogonadism however there is debate as to their role in elderly men with partial, age related decreases in testosterone. Potential benefits must be weighed against the risks (See Tables 4 & 5). {Prevalence of age-related low testosterone in males: age 40-50yr = 7%; age 60-80yr = 20%; age >80yr ≥35%} [6]

In true hypogonadism, adverse effects of androgen therapy are very rare.[7] The risk of most concern is that of an adverse effect on the prostate. Androgens are involved in growth of prostate nodules, hyperplasia and carcinoma; however, observational studies have not demonstrated a consistent role for testosterone in the development of prostate cancer.[2] **Ruling out prostate cancer** (1 in 8 men will develop in their lifetime, mostly after age 70 [8]) is a prerequisite of therapy.

To date trials are limited in that they have involved small numbers, been relatively short term (up to 3 years), and included healthy men with few or no signs of prostate disease (see Table 2).[1,2] **No trials are of significant size to provide reliable information on long-term cardiovascular or prostate outcomes**. Large-scale trials are being considered.[9] Given the limited evidence, androgen therapy of PADAM should be cautiously approached.[1,6,7,10] Benefits may outweigh risks in patients with more severe symptoms of androgen deficiency. The recent Women's Health Initiative (WHI [11]) showed that predictions based on theoretical and observational data may not hold up in a well designed large-scale randomized clinical trial. **Androgens Chart – Table 3**

Table 2: Controlled trials of testosterone (T) therapy in adult males with low-normal T levels (minimum 3months duration; at least 40 subjects)

Study	Size; Age ave	Duration		Therapy Studied	Effect	Adverse Effects
Janowsky 1994 [12]	**n=56**; **67yr** T_{mean} = ? nmol/l	**3** month	PLACEBO Controlled	**T-scrotal patch** 15mg/day vs Placebo	◆ ↑ LBM & ↓ in fat mass [13,17] ◆ BMD: ↑ [17] or no change [14]; subanalysis found ↑BMD in ♂ with T ≤6.9nmol/L [14] ◆ Strength: no change [13,17]; improvement in perception but not actual physical function [13] ◆ Sexual function: no change [12] or slight improvement [20] ◆ CV: ↓ exercise induced angina & pain [16] ◆ Mood/energy/wellbeing: no effect [12,19]; ↑ [16] ◆ Cognition: improved – spatial only [12]	◆ ↑ PSA: usually small but consistent; generally no change IPSS or prostate weight (↑ $PSA^{2⇨2.6ug/L}$) [17] ◆ ↑Hct >52% in 6-11% of pts [13,22] & Hgb ◆ HDL no change [15] or slight ↓ [18]; ◆ CV events: unknown (16 vs 9% for T vs Pl; p=0.25 NS) [15] ◆ skin irritation: 77% Patch vs 40% Pl [17] ◆ High Dose Gel [23]: ↑Hct; ↓HDL ◆ Gel tolerated better vs patch [24] (skin irritation on patch 21%) ◆ gynecomastia (1.8%) [21]
Snyder 1999 [13,14],01 [15]	**n=108**; **73yr** T_{mean} =12.7 nmol/l	**36** month		**T-scrotal patch** 6mg/day vs Placebo (TESTODERM)		
English 2000 [16]	**n=46**; **62yr** T_{mean} =13.5 nmol/l	**3** month		**T-transdermal** patch 5mg/day vs Placebo (in ♂ with coronary artery disease)		
Kenny 2001 [17],02 [18,19]	**n=67⇨44**; **76yr** T_{mean} =13.5 nmol/l	**12** month		**T-transdermal** patch 5mg/day vs Placebo (also Ca^{++} 500mg +Vit. D 400 IU/d)		
Kunelius 2002 [20]	**n=120**; **58yr** T_{mean} =16 nmol/l	**6** month		**DHT gel 125-250mg/d** vs Placebo ◆ **all 6 dropouts on DHT!**		
Wang 2000 [21,22],01 [23]	**n=227**; **51yr** (<52% age ≥50yr) T_{mean}=8.2 nmol/l	**3 & 6** month unblind & dose adjust @3mo	ACTIVE Control	**ANDROGEL 50mg/day** vs **ANDROGEL 100mg/day** blinded vs **ANDRODERM 5mg/day** open label	↑ BMD HD gel, ↓ fat mass Gel groups; ↔ lipids. Over baseline (all groups but not placebo controlled): improved sexual function, mood, strength, & ↑ LBM.	
McNicholas 2003 [24]	**n=208**; **58yr** T_{mean} =7.9 nmol/l	**3** month		**T-gel 50mg/day** (TESTIM) vs **T-gel 100mg/day** blinded vs **T-patch 5mg/day** open label	T gel: ↑ LBM, ↑ positive mood, ↑ libido & sexual function; All arms had ↑LBM. ↔BMD	

♂= male **BMD**= bone mineral density **CV**= cardiovascular **DHT**= dihydrotestosterone **Hct**= hematocrit **HD**= high dose **IPSS**= international prostate symptom score **LBM**= lean body mass **LDL**= low-density lipoproteins **NS**= not significant **PSA**= prostate specific antigen **T**= testosterone (**Range**: **6-29 nmol/L** SK Prov Lab) **TC**= total cholesterol

Table 3 - Testosterone Agents [non-17-α-alkylated]

Prepared by: L. Regier – www.RxFiles.ca – May 03

Route of Administration	Drug	Trade Name	Formulation	Usual Dosage Range (adult men androgen deficiency)	$ /30 days	Comments
ORAL	**Testosterone undecanoate**	ANDRIOL	40mg cap	**80mg AM + 40mg PM** 80mg BID **after meals** (swallow without chewing) 40mg every other day ♀?	**$108** $142 $ 25	◆ taking **after meals** greatly enhances absorption [25] ◆ no effect on liver function over 10yrs (observation)[26] ◆ **Storage**: refrigerate in pharmacy; store at room temperature after dispensing (stable for 90 days)[27]
TRANSDERMAL GEL ✘	**Testosterone 1% Gel** (5g packet delivers 50mg testosterone & approx. 10% absorbed)	ANDROGEL	2.5g, 5g packet	**5g daily in AM** *initial dose ♂* 7.5g daily in AM 10g daily in AM	**$142** $142 $272 ✘	◆ applied to shoulder, abdomen or upper arms ◆ patient should wait >6hrs before showering, etc. ◆ possible transfer to partner ∴T-shirt before hugging ◆ **gel** generally better tolerated than patch
TRANSDERMAL PATCH ✘	**Testosterone** (in alcohol based gel)	ANDRODERM	2.5mg, 5mg patch	2.5mg patch daily at HS **5mg patch daily at HS** 7.5mg patch(s) daily at HS (Apply between 8 & 12 PM)	$142 **$142** $272 ✘	◆ produces stable – normal testosterone levels (8-12hrs after nightly application) ◆ **skin irritation** at site; burn-like blister >10%; if mild may use low potency topical corticosteroid ◆ apply to back, abdomen, thigh or upper arms; avoid bony areas; ROTATE site weekly ◆ contact with water does not affect patch
INJECTABLE **Cost: also consider cost of additional visits to receive injections.**	**Testosterone cypionate**	DEPO-TESTOSTERONE	100mg/ml (10ml Vial)	100mg IM q2wks 150mg IM q2-3wks (Alternating buttocks)	$ 12 $ 15	◆ supratherapeutic levels during first few days; subtherapeutic levels thereafter; ∴more prone to side effects such as mood disturbance, etc. ◆ testosterone levels: 7th day injection (mid range) ◆ range: 50mg q2wk – 200mg q2wk - 400mg q4wks
	Testosterone enanthate	DELATESTRYL [smaller injection volume advantage]	**200mg/ml** (5ml Vial)	100mg IM q2wks 150mg IM q2-3wks 100mg IM q4wks ♀?	$ 14 $ 16 $ 10	

◆ =Exception Drug Status ✘ =non-formulary in Sask ♂ =male; ♀ **=dose in women; {caution - data lacking!** [28] Dose must be individualized}. **Conversion Factor:** Testosterone ng/dL x **0.0347** = nmol/L

Major Contraindications: polycythemia, prostate cancer, prostate hypertrophy with severe urinary retention, testicular or breast cancer **Precautions:** mild prostate hypertrophy, sleep apnea

Goal of Androgen Therapy: primarily to improve symptoms of hypogonadism and to bring T levels into the normal range **Therapeutic Trial Duration:** ≥ 3-6 months

↓ Testosterone Effect: [1,29] **DRUGS**: alcohol, cimetidine, flutamide, glucocorticoids, ketoconazole, opioids, phenytoin, spironolactone; **LIFESTYLE**: smoking, stress, obesity [30]; chronic medical conditions **MEDICAL CONDITIONS**: hypothyroidism, hyperprolactinemia (drug induced or prolactinoma), Klinefelter's syndrome, pituitary adenomas or tumors affecting pituitary (e.g. meningiomas, chromaphobe adenomas)

Related Conditions & Therapies: **DEPRESSION** ⇨ antidepressants, mood stabilizers; **ERECTILE DYSFUNCTION** ⇨ **VIAGRA**, **MUSE**, other; **OSTEOPOROSIS** ⇨ bisphosphonates, Ca^{++} & Vitamin D; **HYPOTHYROIDISM** ⇨ levothyroxine; **LIBIDO** ⇨ multifactorial; **LIFESTYLE** ⇨ exercise, diet, sleep, avoid excess alcohol & caffeine, positive social support/relationships

Table 4: Potential BENEFITS of Androgen Therapy [1,31]

- ↓↓ body fat; ↑ lean body mass (LBM) [36]
- ↑ bone density*; lack data on fracture outcomes
- ↑ hand-grip strength*; (less effect on lower body)
- improvement in mood*; mixed effects on cognition[1]
- antidepressant effect in depressed refractory ≥4 weeks men with low testosterone levels (preliminary data) [37]
- ↑ libido; possible improvement in sexual function but **often not useful in erectile dysfunction** [29] *; {impotence multifactorial and testosterone often not beneficial; one study found placebo (8 wks) as effective as testosterone undecanoate in treating impotence [38]}
- HIV-AIDS patients: improved quality of life, ↑LBM [39,40]

* **(improvements specifically seen in men with the very low/lowest of testosterone levels)**

Table 5: Potential RISKS of Androgen Therapy [10,32,33,34]

- **Cardiovascular - ↓HDL**; long-term effects unknown
- **Fluid retention**; exacerbation of heart failure
- **Polycythemia (↑Hgb; ↑Hct)** – ↑stroke risk; less with oral/ transdermal forms which provide stable levels
- **Gynecomastia** (especially if **hepatic/renal** disease)
- **Prostate:** ↑ prostate size; ↑ PSA but usually within normal range; possible acceleration of prostate cancer; **Difficulty with urination** - 2° to benign prostatic hypertrophy (one study found retardation in BPH [41])
- **Sleep apnea?**– may exacerbate pre-existing sleep apnea ∴caution in obese, smokers, COPD
- **Other**: acne; exacerbation of aggression, hostility, inappropriate sexual behavior or psychotic illness [42]

{Hepatotoxicity only with anabolic 17-α-alkylated forms e.g. stanozolol}

Table 6: MONITORING of Androgen Patients [2,29,35]

- **Clinical evaluation** of symptom response and side effects (from patient and/or spouse or family member)
- **Prostate assessment**: baseline & annually; some references suggest more frequent in first year [2,35]
  - ◆ questionnaire regarding urinary/prostate symptoms
  - ◆ digital rectal exam (DRE) & **PSA** (range: 0-4 ug/L)
- **Lab Tests**: Hct, Hgb, Liver Function Tests
- **CV assessment**: lipid profile, edema, weight gain
- **Testosterone** level (normal = **6-29nmol/L** SK Prov Lab) **Free Androgen Index** ⇨**provides better measure of bioavailable testosterone** (normal ♂ = **14.8-94.8**); (accounts for effect of sex hormone binding globulin SHBG)
- **Sleep** disturbance: excessive snoring; sleep apnea
- **Mood** changes

Recent Drug Therapy Issues

2. Topical Corticosteroids on the Face – *the Cure Becomes the Problem!*

Topical corticosteroids on the face often produce local side effects, including atrophy, steroid acne, **perioral dermatitis**, hypertrichosis, hypopigmentation, rosacea, glaucoma, striae, telangiectasia and superinfections.[43,44,45,46,47] **Steroid-induced rosacea** with **facial use of mid-high potency steroids** has been reported, thus we are strengthening our cautionary statement in the corticosteroid chart. Even the lowest potency topical steroids induced rosacea in a study of 106 children.[48] This study and a recent review recommended abrupt withdrawal of topical steroids and treatment of the rosacea.[44] A severe rebound "flare-up" would be expected, usually in 4-10 days and lasting up to 3 weeks. Treatment depends on the stage: **antibiotics** (oral: tetracycline/doxycycline [adults] or erythromycin [children]; topical: metronidazole or clindamycin [preferred in pregnancy]), retinoids, atenolol, clonidine, tacrolimus, surgery or laser therapy.[49,50,51,52] Treatment of unresponsive steroid-induced rosacea with ≤ 10days of tacrolimus (PROTOPIC 0.03-0.1% ointment BID ~$84/month, EDS Sask) or possibly pimecrolimus (ELIDEL 1% cream BID ~$72/month, non formulary Sask) appears promising. These new agents may cause less skin atrophy, less rebound "flare-up", but may cause some skin burning, itching, and an increased risk of infection. *See previous review - RxFiles – May98.*[53]

BOTTOM LINE: In general, only low potency topical corticosteroids should be used on the face and only for a limited time.

Topical Corticosteroid Creams: Comparison Chart Prepared by Loren Regier, Brent Jensen ***www.RxFiles.ca*** **May 03**

DRUG/STRENGTH C (grouped by formulation & potency)	BRAND NAME	POTENCY & $ Ultra-High----Mid----Low 1 | 2 | 3 | 4 | 5 | 6 | 7	SIZE / COMMENTS	
CREAMS → cause less occlusion, are suitable for non-acute, wet lesions & tend to be cosmetically more acceptable				
Betamethasone dipropionate glycol 0.05%	**Diprolene Glycol, Topilene Glycol** [PB]	$26	15,50g	PG, •
Clobetasol propionate 0.05%	***Dermovate,*** *Others*	$22	15,50g	PG
Desoximetasone 0.25%	*Topicort* [PB, WA] *, Desoxi*	$23	20,60g	•
Fluocinonide 0.05%	*Lidex, Lyderm* *Lidemol (Emollient Base•)*	$24 $27	15,60g	PG •
Halcinonide 0.1%	*Halog*	$26	15,30,60g	PG
Halobetasol propionate 0.05%	*Ultravate* Exception Drug Status in Sask.	$33	15,50g	
Betamethasone dipropionate 0.05%	***Diprosone, Taro-Sone*** [PG]	$15	15,50,450g	•
Amcinonide 0.1%	*Cyclocort* (lanolin,paraben,PG,tartrazine,urea free•)	$25	15,30,60g	OH, •
Beclomethasone dipropionate 0.025%	*Propaderm*	$28	15,45g	OH
Clobetasone butyrate 0.05%	*Eumovate*	$22	15,30g	
Desoximetasone 0.05%	*Topicort Mild* [PB, WA] *, Desoxi*	$17	20,60g	•
Diflucortolone valerate 0.1%	*Nerisone Cr* [PB] *, Nerisone Oily Cr* (NP)	$21	30g	•
Mometasone furoate 0.1%	*Elocom* (**Once daily** recommended)	$30	15,50,100g	PG
Triamcinolone acetonide 0.1%	*Kenalog, Triaderm, Aristocort-R* R=reg	$13	15,30,500g	PG
Betamethasone valerate 0.1% **0.05%**	***Betaderm*** [PG] ***, Celestoderm-V, Ectosone*** [PB] ***Betaderm*** [PG] ***,Celestoderm-V/2,Ectosone Mild*** [PB]	$8	15,~450g	• low cost
Fluocinolone acetonide 0.025% 0.01%	*Fluoderm regular* *Fluoderm mild*	$19 $10	15,500g	PG, PB
Hydrocortisone valerate 0.2%	*Westcort , Hydroval* [PB]	$14	15,45,60g	PG, •
Triamcinolone acetonide 0.025%	*Triaderm*	$9	15,30,500g	PG
Desonide 0.05%	*Desocort, Tridesilon*	$17	15,60g	PG
Hydrocortisone/**Urea** 1%/10%	*Uremol-HC*	$14	50,225g	PG ;8-15°C
Hydrocortisone 2.5% **1%** **0.5% (OTC)**	***Emo-Cort*** ***Cortate, Hyderm, Emo-Cort*** *Cortate, Hyderm, Unicort,* others	$15 $8 $13	45,225g 15,~450g	OD-QID low cost

***Low Potency*: preferred when necessary on thin skin areas, in elderly, young children or infants or if used long-term. Caution if on face or thin skin areas!**

***High Potency* agents: reserve for resistant conditions/ thick skin areas due to potential for local & systemic side effects.**
***Ultra Potent* agents:**
• max ~50g/week;
• limit duration
• apply OD-BID

Cost = cost for **30g** (incl. markup/dispensing fee) in Sask. Lowest price alternative used where available **EDS**= Exceptional Drug Status Note: **Ointments more potent than creams!**
• = brand specific info in brand section; **OH** = benzyl or isopropyl alcohol; **NP** = no preservatives; **PB** = parabens; **PG** = propylene glycol; **WA** = wool alcohol

Potency * Classification - Ultra high potency steroids are up to 1000 times more potent than hydrocortisone [44]	
Group 1 = Ultra High Potency	•reserve **for resistant conditions**; high potential for serious side effects (local & systemic) •suitable for **short term** intermittent use in severe eczematous dermatoses and psoriasis •often required for palms, soles, & scalp where thickened skin may require prolonged Tx
Group 2,3 = High Potency	•generally limit to OD-BID, & length of Tx. to **≤2-4 weeks** followed by less potent agent •**avoid** use on large areas, thin skin areas, skin folds, in young children/infants, face
Group 4,5 = Mid Potency	•suitable for intermittent long term use, chronic use in thick skin areas (hand eczema) • **avoid** on thin skin areas; **extreme caution** if used on **face**, intertriginous areas (severe adverse effects)
Group 6,7 = Low Potency	•safest for use in children, infants, & elderly or when covering large or higher risk areas (face, eyelids, skin flexures, scrotum); **CAUTION** still required! •suitable for **maintenance** of most chronic conditions after initial control obtained •often applied BID-QID; apply less frequent (OD-BID) if ongoing use

*Actual potency may vary considerably depending on: site of application, skin condition, use of occlusion, & individual patient variation.

3. SaskAR - Saskatchewan Regional Adverse Reaction Reporting Centre

Did you know???

- **51%** of newly approved drugs have serious adverse effects that are **undetected** at the time of marketing.[54]
- **3-7%** of hospital admissions are due to adverse reactions[55,56,57,58,59,60,61] and **1.5-35%** of patients experience a 2nd reaction during hospital stay.[55-58,62,63,64]
- Adverse reactions are reported in:
  6% of patients taking **1-3 medications** and in **52%** of patients taking **8 or more medications.**[65]
- The reported incidence of adverse reactions in ambulatory patients varies from **3-68%.**[66,67]
- A study done by Canadian investigators at the University of Toronto showed serious ARs result in **76,000-137,000 deaths** annually in the United States, making ARs the 4th to 6th leading U.S. cause of death.[68]

Why is it important to document adverse reactions?

- Knowledge of drug risk evolves over the lifetime of the drug and therefore risk assessment must continue beyond the pre-market evaluation phase.
- Populations used in clinical trials are not representative of the population as a whole. "Clinical trials evaluate drugs rather than patients or diseases." [69]
- Spontaneous, voluntary reporting programs (e.g. SaskAR) serve as "early warning systems" for rare and unexpected reactions. These programs have been credited with **initial detection** of thromboembolic complications with oral contraceptives, withdrawal reactions to paroxetine, hepatotoxicity with nefazodone, and drug interactions with grapefruit juice.
- Case reports are reviewed and entered onto national and international databases that are constantly monitored for signals. Serious, unlabelled effects, **if reported,** become known very quickly allowing for timely notification of health care professionals.

What is an Adverse Reaction (AR)?

Health Canada defines an AR as "a noxious and unintended response to a drug which occurs with use or testing for the diagnosis, treatment, or prophylaxis of a disease or modification of an organic function. This includes **any** undesirable patient effect suspected to be associated with drug use. ARs resulting from any prescription, non-prescription, biological (including blood products), complementary medicines (including herbals), and radiopharmaceutical drug products are monitored." [70]

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***Brent Jensen** BSP, **Loren Regier** BSP,BA*

AR reports are, for the most part, only **SUSPECTED** associations! Reporting an AR does not imply a causal link.

What kind of adverse reactions should I report?

A temporal or possible association is sufficient for a report to be submitted.

The following suspected reactions should be reported:

- **Reactions to Recently Marketed Drugs**
  includes drugs that have been marketed within the last **5 years**. All reactions, regardless of nature or severity, should be reported as these drugs have limited post-marketing experience.
- **Serious Reactions**
  includes reactions that result in hospitalization or prolong existing hospitalization, results in congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death.
  report serious reactions **when they occur** even if all details are not known. Follow-up information can be submitted when it becomes available.
- **Unexpected Reactions**
  includes reactions (regardless of severity) which are not consistent with product labeling. These reactions are often NOT explainable pharmacologically.

REPORTING AN ADVERSE REACTION

Reports can be submitted in writing (i.e. by mail or fax) or verbally by telephone (Hours: Monday-Friday, 0830-1630).

FAX - Saskatoon	**306-966-2286**
FAX - Toll-free Canada	**1-866-678-6789**
Telephone - Saskatoon	**306-966-6329**
Telephone - Toll-free Canada	**1-866-234-2345**

Report forms are available in:

- Compendium of Pharmaceuticals & Specialties (CPS)
- Saskatchewan Prescription Drug Plan Formulary Appendix
- Health Canada website
  http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/adr.html
  Click on "Report (form) of suspected adverse reaction due to drug products marketed in Canada". Form can be downloaded, printed, completed and sent.

If you have any comments or questions, or if you would like to report an adverse reaction, please contact us.

SaskAR Regional Centre, Saskatchewan Drug Information Service (SDIS), College of Pharmacy & Nutrition, 110 Science Place, University of Saskatchewan, Saskatoon SK S7N 5C9
Telephone: Saskatoon 306-966-6329; Toll-free 1-866-234-2345

Physician, reporter & patient confidentiality is ensured.

Regular advisories by Health Canada can be obtained from http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/adviss_tpd_bgtd_e.html
Email service provides link to free advisories upon posting.

Health Canada / Santé Canada

Canadian Adverse Drug Reaction Monitoring Program

Report of suspected adverse reaction due to drug products marketed in Canada (Vaccines excluded)

Therapeutic Products Programme

PROTECTED

- **See reverse for return address.**
- **La version française de ce document est disponible sur demande. Voir au verso pour connaître le centre à contacter.**

A. Patient Information

1. Patient identifier	2. Age at time of reaction	3. Sex	4. Height	5. Weight
	_____ or	☐ Male	_____ feet	_____ lbs
Chart Number	**Date of birth** DD / MM / YYYY	☐ Female	or _____ cm	or _____ kgs

B. Adverse Reaction

1. Outcome attributed to adverse reaction (check all that apply)

- ☐ Death _____ (dd / mm / yyyy)
- ☐ Disability
- ☐ Life-threatening
- ☐ Congenital malformation
- ☐ Hospitalization
- ☐ Required intervention to prevent damage / permanent impairment
- ☐ Hospitalization - prolonged
- ☐ Other: _____

2. Date and time of reaction DD / MM / YYYY

3. Date of this report DD / MM / YYYY

4. Describe reaction or problem

5. Relevant tests / laboratory data (including dates (dd / mm / yyyy)

6. Other relevant history, including preexisting medical conditions (e.g. allergies, pregnancy, smoking and alcohol use, hepatic / renal dysfunction)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the adverse reaction.

C. Suspected drug product(s) (See "How to report" section on reverse)

1. Name (give labelled strength & manufacturer, if known).

#1 _____

#2 _____

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)
#1	#1 From (dd / mm / yyyy) - To (dd / mm / yyyy)
#2	#2

4. Indication for use of suspected drug product	5. Reaction abated after use stopped or dose reduced
#1	#1 ☐ Yes ☐ No ☐ Doesn't apply
#2	#2 ☐ Yes ☐ No ☐ Doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Reaction reappeared after reintroduction
#1 _____	#1 (dd / mm / yyyy) _____	#1 ☐ Yes ☐ No ☐ Doesn't apply
#2	#2	#2 ☐ Yes ☐ No ☐ Doesn't apply

9. Concomitant drugs (name, dose, frequency and route used) and therapy dates (dd / mm / yyyy) (exclude treatment of reaction)

10. Treatment of adverse reaction (drugs and / or therapy), **including dates** (dd / mm / yyyy)

D. Reporter (See "Confidentiality" section on reverse)

1. Name, address & phone number.

2. Health professional?	3. Occupation	4. Also reported to manufacturer?
☐ Yes ☐ No		☐ Yes ☐ No

For TPP use only

Canada

References – 1. Androgens & the Aging Male; 2. Topical Corticosteroids on the Face; 3. AR Reporting - www.RxFiles.ca - May 2003

ANDROGENS…

[1] Gruenewald DA, Matsumoto AM. Testosterone Supplementation Therapy for Older Men: Potential Benefits and Risks. J Am Geriatr Soc. 2003 Jan;51(1):101-115.
[2] Morales A, Tenover JL. Androgen deficiency in the aging male: when, who, and how to investigate and treat. Urol Clin North Am. 2002 Nov;29(4):975-82.
[3] Howell SJ, Radford JA, Adams JE, Smets EM, Warburton R, Shalet SM. Randomized placebo-controlled trial of testosterone replacement in men with mild Leydig cell insufficiency following cytotoxic chemotherapy. Clin Endocrinol (Oxf). 2001 Sep;55(3):315-24.
[4] Perry PJ, Lund BC, Arndt S, Holman T, et al. Bioavailable testosterone as a correlate of cognition, psychological status, quality of life, and sexual function in aging males: implications for testosterone replacement therapy. Ann Clin Psychiatry. 2001 Jun;13(2):75-80.
[5] Morley JE, Charlton E, Patrick P, Kaiser FE, et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism. 2000 Sep;49(9):1239-42.
[6] Casey RW. COUNTERPOINT: Urologists should take an active role in the diagnosis and treatment of hypogonadism in the aging male. Can J Urol. 2002 Dec;9(6):1681-3.
[7] Juul A, Skakkebaek NE. Androgens and the ageing male. Hum Reprod Update. 2002 Sep-Oct;8(5):423-33.
[8] Canadian Cancer Statistics 2003, http://www.cancer.ca/ccs/internet/standard/0,2283,3172_14471__langId-en,00.html ,accessed Apr/03.
[9] Reuters Health Information: Institute of Medicine Panel Mulls Testosterone Replacement Questions. Available 2/5/2003.
[10] Report of National Institute on Aging Advisory Panel on Testosterone Replacement in Men. J Clin Endocrinol Metab. 2001 Oct;86(10):4611-4.
[11] Writing Group for the Women's Health Initiative (**WHI**) Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women - Principal Results From the Women's Health Initiative Randomized Controlled Trial. JAMA 2002;288: 21-333.
[12] Janowsky JS, Oviatt SK, Orwoll ES. Testosterone influences spatial cognition in older men. Behav Neurosci. 1994 Apr;108(2):325-32
[13] Snyder PJ, Peachey H, Hannoush P, Berlin JA, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab. 1999 Aug;84(8):2647-53.
[14] Snyder PJ, Peachey H, Hannoush P, Berlin JA, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab. 1999 Jun;84(6):1966-72.
[15] Snyder PJ, Peachey H, Berlin JA, Rader D, et al. Effect of transdermal testosterone treatment on serum lipid and apolipoprotein levels in men more than 65 years of age. Am J Med. 2001 Sep;111(4):255-60.
[16] English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. Circulation. 2000 Oct 17;102(16):1906-11.
[17] Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci. 2001 May;56(5):M266-72.
[18] Kenny AM, Prestwood KM, Gruman CA, Fabregas G, Biskup B, Mansoor G. Effects of transdermal testosterone on lipids and vascular reactivity in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci. 2002 Jul;57(7):M460-5.
[19] Kenny AM, Bellantonio S, Gruman CA, Acosta RD, Prestwood KM. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci. 2002 May;57(5):M321-5.
[20] Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. J Clin Endocrinol Metab. 2002 Apr;87(4):1467-72.
[21] Wang C, Swedloff RS, Iranmanesh A, Dobs A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group. J Clin Endocrinol Metab. 2000 Aug;85(8):2839-53.
[22] Swerdloff RS, Wang C, Cunningham G, Dobs A, et al. Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. J Clin Endocrinol Metab. 2000 Dec;85(12):4500-10.
[23] Wang C, Swerdloff RS, Iranmanesh A, et al. Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men. Clin Endocrinol (Oxf) 2001 Jun;54:739-50.
[24] McNicholas TA, Dean JD, Mulder H, Carnegie C, Jones NA. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. BJU Int. 2003 Jan;91(1):69-74.
[25] Bagchus WM, Hust R, Maris F, Schnabel PG, Houwing NS. Important effect of food on the bioavailability of oral testosterone undecanoate. Pharmacotherapy. 2003 Mar;23(3):319-25.
[26] Gooren LJ. A ten-year safety study of the oral androgen testosterone undecanoate. J Androl. 1994 May-Jun;15(3):212-5.
[27] Bagchus WM, Hust R, Maris F, Schnabel P, Houwing N. Important Effect of Food on the Bioavailablility of Oral Testosterone Undecanoate. Pharmacotherapy 2003;23 (3):319-326.
[28] Padero MC, Bhasin S, Friedman TC. Androgen supplementation in older women: too much hype, not enough data. J Am Geriatr Soc. 2002 Jun;50(6):1131-40.
[29] Tenover L. Male Hormone Replacement Therapy Including "Andropause". Endocrin and Metab Clinics of N America 1998;27(4):969-87.
[30] Vermeulen A. Decreased androgen levels and obesity in men. Ann Med. 1996 Feb;28(1):13-5.
[31] Wang C, Eyre DR, Clark R, Kleinberg D, et al. Sublingual testosterone replacement improves muscle mass and strength, decreases bone resorption, and increases bone formation markers in hypogonadal men--a clinical research center study. J Clin Endocrinol Metab. 1996 Oct;81(10):3654-62.
[32] Heaton JP. POINT: Urologists should take an active role in the diagnosis and treatment of hypogonadism in the aging male. Can J Urol. 2002 Dec;9(6):1677-80.
[33] Wespes E, Schulman CC. Male andropause: myth, reality, and treatment. Int J Impot Res. 2002 Feb;14 Suppl 1:S93-8.
[34] Report of National Institute on Aging Advisory Panel on Testosterone Replacement in Men. J Clin Endocrinol Metab. 2001 Oct;86(10):4611-4.
[35] Stas SN, Anastasiadis AG, Fisch H, Benson MC, Shabsigh R. Urologic aspects of andropause. Urology. 2003 Feb;61(2):261-6.
[36] Bhasin S, Bagatell CJ, Bremner WJ, Plymate SR, et al. Issues in testosterone replacement in older men. J Clin Endocrinol Metab. 1998 Oct;83(10):3435-48.
[37] Pope HG Jr, Cohane GH, Kanayama G, et al. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. Am J Psychiatry 2003 Jan;160:105-11.
[38] Benkert O, Witt W, Adam W, Leitz A. Effects of testosterone undecanoate on sexual potency and the hypothalamic-pituitary-gonadal axis of impotent males. Arch Sex Behav. 1979 Nov;8(6):471-9.
[39] Fairfield WP, Treat M, Rosenthal DI, Frontera W, Stanley T, Corcoran C, Costello M, Parlman K, Schoenfeld D, Klibanski A, Grinspoon S. Effects of testosterone and exercise on muscle leanness in eugonadal men with AIDS wasting. J Appl Physiol. 2001 Jun;90(6):2166-71.
[40]Bhasin S, Storer TW, Asbel-Sethi N, Kilbourne A, et al. Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. J Clin Endocrinol Metab. 1998 Sep;83(9):3155-62.
[41] Pechersky AV, Mazurov VI, Semiglazov VF, Karpischenko AI, Mikhailichenko VV, Udintsev AV. Androgen administration in middle-aged and ageing men: effects of oral testosterone undecanoate on dihydrotestosterone, oestradiol and prostate volume. Int J Androl. 2002 Apr;25(2):119-25.
[42] Weiss EL, Bowers MB Jr, Mazure CM. Testosterone-patch-induced psychotic mania. Am J Psychiatry. 1999 Jun;156(6):969.

TOPICAL CORTICOSTEROIDS…

[43] Lee NP, Arriola ER. Topical corticosteroids: back to basics. West J Med. 1999 Nov-Dec;171(5-6):351-3.
[44] Dubertret L. Which steroids for the treatment of skin disorders on the face? J Eur Acad Dermatol Venereol. 2002 Mar;16(2):121.
[45] Furue M, Terao H, Rikihisa W, Urabe K, et al Clinical dose and adverse effects of topical steroids in daily management of atopic dermatitis. Br J Dermatol. 2003 Jan;148(1):128-33.
[46] Aggarwal RK, Potamitis T, Chong NH, Guarro M, Shah P, Kheterpal S. Abstract, Extensive visual loss with topical facial steroids. Eye 1993;7 (Pt 5):664-6.
[47] Litt JZ. Abstract, Steroid-induced rosacea. Am Fam Physician. 1993 Jul;48(1):67-71.
[48] Weston WL, Morelli JG. Steroid rosacea in prepubertal children. Arch Pediatr Adolesc Med. 2000 Jan;154(1):62-4.
[49] Blount BW, Pelletier AL. Rosacea: a common, yet commonly overlooked, condition. Am Fam Physician. 2002 Aug 1;66(3):435-40.
[50] Rebora A. The Management of Rosacea. Am J Clin Dermatol. 2002;3(7):489-96.
[51] Barankin B, Guenther L. Rosacea and atopic dermatitis. Two common oculocutaneous disorders. Can Fam Physician. 2002 Apr;48:721-4.
[52] Goldman D. Tacrolimus ointment for the treatment of steroid-induced rosacea: a preliminary report. J Am Acad Dermatol. 2001 Jun;44(6):995-8.
[53] Regier L, Downey S. Topical Corticosteroids. RxFiles May 1998. Available at http://www.rxfiles.ca/acrobat/top%2Dcort.pdf & http://www.rxfiles.ca/acrobat/CHT-SteroidClassPotencyCOLOR.pdf

AR REPORTING…

[54] Moore T, Psaty B, Furberg C. Time to act on drug safety. *JAMA* 1998; 279(19):157-73.
[55] Karch FEW, Lasagna L. Adverse drug reactions: a critical review. *JAMA* 1975; 234; 1236-41.
[56] McKenney JM, Harrison WL. Drug-related hospital admissions. *Am J Hosp Pharm* 1976; 32; 792-5.
[57] Hallas J et al. Drug-related hospital admissions: The role of definition and intensity of data collection and the possibility of prevention. *J Intern Med* 1990; 228; 83-90.
[58] Leape LL, Brennan TA, Larird et al. The nature of adverse events in hospitalized patients: Results of the Harvard Medical Practice Study II. *N Engl J Med* 1991; 324; 377-84.
[59] Einarson TR. Drug-related hospital admissions. *Ann Pharmacother* 1993; 27; 832-40.
[60] Dartnell JG, Crowe DM, Schubert AL, Molds RG. Review of use of adverse drug reaction labels on medical records. *Aust J Hosp Pharm* 1994; 24; 333-5.
[61] Gruchalla RS. Clinical assessment of drug-induced disease. *The Lancet* 2000; 356;1505-1511.
[62] Seidl LG, Thornton GF, Smith JW, et al. Studies on the epidemiology of adverse drug reactions, iii; Reactions in patients on a general medical service. *Bull John Hopkins Hospital* (Nov 1996);119:299-315.
[63] Smith LG, Seidl LG, Cluff LE. Studies on the epidemiology of adverse drug reactions v. Clinical factors influencing susceptibility. *Ann Intern Med*. (Oct 1996);65:629-40.
[64] Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse events. Implications for prevention. *JAMA*. 1995;274(1):29-34.
[65] Finchem JE. An overview of adverse drug reactions. *American Pharmacy*. 1991;NS31 (6):47-52.
[66] Martys CR. Adverse reactions to drugs in general practice. *BMJ*. 1997;2:1194-97.
[67] Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med*. 2003;348:1556-64.
[68] Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. *JAMA*. 1998;279:1200-1205.
[69] Figueras A, Laporte J-R. Failures of the therapeutic chain as a cause of drug ineffectiveness. *BMJ*.2003;326:895-6.
[70] Health Canada Guidelines for Reporting Adverse Reactions to Marketed Drugs available at: http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/guides/adr/adr_guideline_e.html